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(71) Applicant: GRUPPO LEPETIT S.P.A.
8, Via Roberto Lepetit
I-20124 Milano(IT)

(72) Inventor: Malabarba, Adriano
5-A, Via Roma
20082 Binasco Milano(IT)
Inventor: Tarzia, Giorgio
23, Via Valletta
21047 Saronno Varese(IT)

(54) Amides of teicoplanin compounds.

(57) The present invention relates to amide derivatives of teicoplanin compounds.

Teicoplanin is an antibiotic substance active mainly against gram-positive bacteria and its derivatives, which are collectively named "teicoplanin compounds", are the components, pseudoaglycones and aglycone thereof.

The compounds of the invention are obtained according to a proper amidation process and are active as antibiotics.

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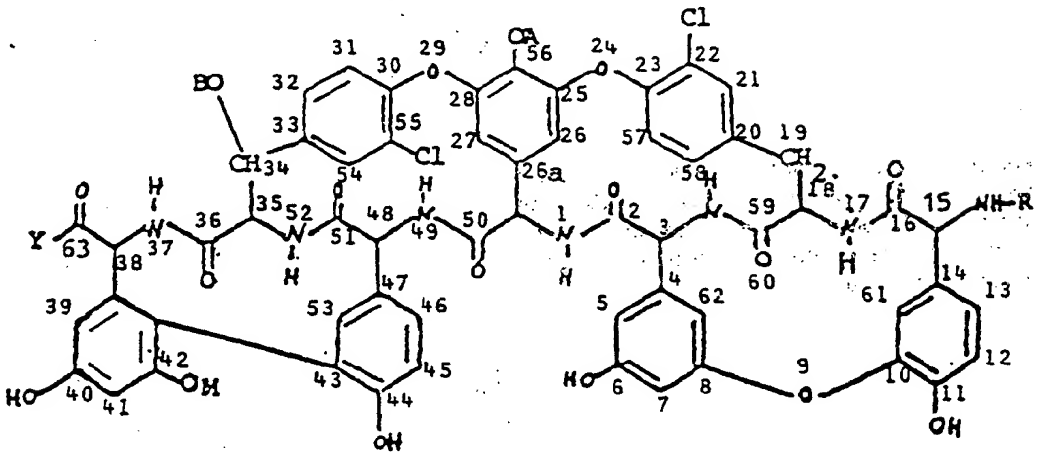
AMIDES OF TEICOPLANIN COMPOUNDS

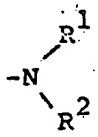
The present invention is directed to amides of teicoplanin compounds having the following formula I:



wherein

R represents hydrogen or a protecting group of the amine function

Y represents a group



wherein

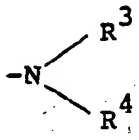
R' represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl, halogeno(C_2-C_4)alkyl, (C_1-C_4)alkoxy(C_2-C_6)-alkyl, amino(C_2-C_4)alkyl, (C_1-C_4)alkylamino(C_2-C_6)-alkyl, di(C_1-C_4)alkylamino(C_2-C_4)alkyl

R^2 represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl, halogeno(C_2-C_4)alkyl, (C_1-C_4)alkoxy(C_2-C_4)-alkyl, a nitrogen containing 5-6 membered heterocyclic ring

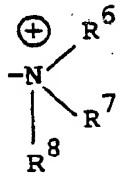
which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents and one of the ring nitrogens may optionally bear a substituent R^3 selected from (C_1-C_4)alkyl, (C_4-C_7)cycloalkyl, phenyl optionally substituted with halogen or (C_1-C_4)alkyl, phenyl(C_1-C_4)alkyl, pyridyl, (C_1-C_4)alkylpyridinio, and when the ring is wholly saturated two of the ring members may optionally be bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N[-(C_1-C_4)alkyl];

a group -alk-W wherein "alk" represents a linear alkylene chain of 1 to 8 carbon atoms which is optionally substituted with a substituent selected from (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, hydroxy, carboxy, aminocarbonyl, (C_1-C_4)alkylaminocarbonyl, di-(C_1-C_4)alkylaminocarbonyl, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, and W represents a carboxy, (C_1-C_4)alkoxycarbonyl, pheny(C_1-C_4)-alkoxycarbonyl, aminocarbonyl, (C_1-C_4)-

aminocarbonyl, di(C_1-C_4)aminocarbonyl, pentosaminocarbonyl, hexosaminocarbonyl, uridino, guanidino, a nitrogen containing 5-6 membered heterocyclic ring defined as above, a group of the formula



wherein R^3 and R^4 each independently represent hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl and halogeno(C_2-C_4)alkyl, or R^4 represents phenylmethyloxycarbonyl and R^3 represents hydrogen; a group of the formula



wherein R^6, R^7 and R^8 each independently represents a (C_1-C_4)alkyl,

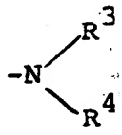
or R^1 and R^2 taken together with the adjacent nitrogen atom represent a saturated 5-7 membered heterocyclic ring which may optionally bear one to two (C_1-C_4)alkyl substituents on the ring carbons and may contain a further heterogroup selected from -O-, -S-, and -NR^5-wherein R^5 is defined as above;

A represents hydrogen or -N[(C_{10}-C_{11})-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl,

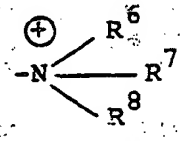
B represents hydrogen or N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl; with the proviso that B represents hydrogen only when A and M are simultaneously hydrogen and M represents hydrogen only when A is hydrogen and with the further proviso that when W represents

a group



a group



ureid , guanidino

or a nitrogen containing 5-6 membered heterocyclic ring as defined above directly connected with the "alk" moiety through a bond with a ring nitrogen atom, the linear alkylen "alk" moiety must be of at least two carbon atoms;

and the addition salts thereof.

Teicoplanin is the international non-proprietary name (INN) of the antibiotic substance formerly named teichomycin which is obtained by cultivating the strain Actinoplanes teichomyceticus nov. sp. ATCC 31121 in a culture medium containing assimilable sources of carbon, nitrogen and inorganic salts (see U.S. Patent No. 4,239,751). According to the procedure described in the above cited patent an antibiotic complex containing Teichomycin A_1, A_2 and A_3 is recovered from the separated fermentation broth by extraction with a suitable water insoluble organic solvent and precipitation from the extracting solvent according to common procedures. Teichomycin A_2, which is the major factor of the isolated antibiotic complex, is then separated from the other factors by means of column chromatography on Sephadex®. British Patent Application Publication No. 2121401 discloses that antibiotic Teichomycin A_2 actually is a mixture of five closely related co-produced main components.

According to recent structural studies it is possible to represent teicoplanin A_2 (formerly Teichomycin A_2) main components 1, 2, 3, 4 and 5 by the above formula I wherein R is hydrogen, Y is hydroxy, A represents -N[(C_{10}-C_{11})-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl, B represent N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl, M represents α-D-manno-pyranosyl.

More particularly, in teicoplanin A_2 component 1, the [(C_{10}-C_{11})-aliphatic acyl] substituent represents Z-decenoyl, in teicoplanin A_2 component 2 represents 8-methyl-nonanoyl, in teicoplanin A_2 component 3 represents decanoyl, in teicoplanin A_2 component 4 represents 8-methyldecanoyl, in teicoplanin A_2 component 5 represents 9-methyl-decanoyl.

All the sugar moieties, when present, are linked to the teicoplanin nucleus through O-glycosidic bonds.

In addition, it has been found that it is possible to transform teicoplanin, a pure factor thereof or a mixture of any of said factors in any proportion, into unitary antibiotic products by means of selective hydrolysis of one or two sugar moieties. They are named antibiotic L 17054 and antibiotic L 17046 and are described in European Patent Application Publication No. 119575 and European Patent Application Publication No. 119574, respectively. Preferred hydrolysis conditions for the production of antibiotic L 17054 are: 0.5 N hydrochloric acid at a temperature between 70°C and 90°C and for a time which is generally between 15 and 90 min.

Antibiotic L 17054 is represented by the above formula I wherein Y is hydroxy, R and A represent hydrogen, B represents N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl, M represents α-D-mannopyranosyl wherein the sugar moieties are linked to the peptidic nucleus through an O-glycosidic bond.

Preferred hydrolysis conditions for the preparation of antibiotic L 17046 are: 1-3 N hydrochloric acid, at a temperature between 50° and 90°C and for a time which is generally between 30 and 60 min.

Antibiotic L 17046 is represented by the above formula I wherein Y is hydroxy, R, A and M represent hydrogen atoms and B is N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl wherein the sugar moiety is linked to the peptidic nucleus through an O-glycosidic bond.

The complete selective cleavage of all the sugar moieties of the teicoplanin compounds gives an aglycone molecule which is called antibiotic L 17392, or deglucoteicoplanin, and is represented by the above formula I wherein Y is hydroxy, and R, A, B, and M each individually represents a hydrogen group. This selective hydrolysis process is described in European patent application No. 84114558.4.

A substance having the same structural formula is disclosed in European Patent Application Publication No. 0090578 and is named antibiotic A 41030 factor B.

This substance is obtained by means of a microbiological process which involves the fermentation of the strain Streptomyces virginie NRRL 12525 or Streptomyces virginiae NRRL 15156 in a suitable medium, the isolation, purification and separation into its components of antibiotic A 41030, an antibiotic complex of at least seven factors, antibiotic A 41030 factor B, included.

All the above named compounds, i.e. teicoplanin, teicoplanin A_2 complex, teicoplanin A_2 component 1, teicoplanin A_2 component 2, teicoplanin A_2 component 3, teicoplanin A_2 component 4, teicoplanin A_2 component 5, antibiotic L 17054, antibiotic L 17046, antibiotic L 17392 and any mixture thereof in any proportion, are suitabl starting materials for the preparation of the amide derivatives of the invention.

In the present specification "teicoplanin compound " or "teicoplanin starting material" is used to in-

dicate any one of the above starting materials, i.e. teicoplanin as obtained according to U.S. patent 4,239,751, any further purification thereof, teicoplanin A_2 complex, a compound of the above formula I wherein R is hydrogen, Y is hydroxy, A represents hydrogen or -N[(C_{10}-C_{11})aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl, B represent hydrogen or N-acetyl-β-D-2-deoxy-2-deoxy-2-amino-glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl, with the proviso that B may represent hydrogen only when A and M are simultaneously hydrogen and M may represent hydrogen only when A is hydrogen, a salt thereof, or a mixture thereof in any proportion.

As used herein the term "alkyl" either alone or in combination with other substituents, includes both straight and branched hydrocarbon groups; more particularly, "(C_1-C_6)alkyl" represents a straight or branched aliphatic hydrocarbon chain of 1 to 6 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 1-hexanyl, 2-hexanyl, 3-hexanyl, 3,3-dimethyl-1-butanyl, 4-methyl-1-pentanyl and 3-methyl-1-pentanyl; likewise, "(C_1-C_4)alkyl" represents a straight or branched hydrocarbon chain of 1 to 4 carbon atoms such as those alkyl of 1 to 4 carbons exemplified above. The term "halogeno" represents an halogen atom selectedf from fluorine, chlorine, bromine and iodine.

The pentosamino moieties of the pentosaminocarbonyl substituent are 2-or 3-amino (2-or 3-deoxy) either D or L or D, L pentose group in either anomeric form or in an anomeric mixture, such as 2-or 3-amino(2-or 3-deoxy)-ribose, 2-or 3-amino(2-or 3-deoxy)arabinose, 2-or 3-amino(2-or 3-deoxy)-xylose and 2-or 3-amino (2 or 3-deoxy)lyxose.

The hexosamino moieties of the hexosaminocarbonyl substituent are either D or L, or D, L) 2-or 3-amino (2-or 3-deoxy)hexose group in either anomeric form or in an anomeric mixture such as 2-or 3-amino(2-or 3-deoxy)allose, 2-or 3-amino(2-or 3-deoxy)altrose, 2-or 3-amino(2-or 3-deoxy)glucose, 2-or 3-amino(2-or 3-deoxy)mannose, 2-or 3-amino-(2-or 3-deoxy)gulose, 2-or 3-amino(2-or 3-deoxy)-galactose, and 3-or 4-amino(2-or 3-deoxy)-fruttofuranose.

"Linear alkylene chains of 1 to 8 carbon atoms" as defined in the present application are straight alkylene chains of 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms. Representative examples of linear alkylene chains of 1 to 6 carbon atoms are:

$-CH_2-$

$-CH_2-CH_2-$

$-CH_2-CH_2-CH_2-$

$-CH_2-CH_2-CH_2-CH_2-$

$-CH_2-CH_2-CH_2-CH_2-CH_2-$

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$

$-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-$

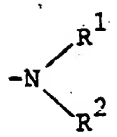
These linear alkylene chain optionally may bear substituents as described above.

The expression "a nitrogen containing 5-6 membered heterocyclic ring which may contain 1 to 3 further heteroatoms selected from N, S, and O" according to the present invention includes unsaturated, partially saturated and wholly saturated ring systems such as pyridinyl, pyrimidinyl, pyrazinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazolyl, oxazolinyl, oxazolidinyl, pyrazolinyl, pyrazolidinyl, thiazolidinyl, morpholinyl, thiomorpholinyl, pyrrolyl, pyrrolinyl, imidazoyl, imidazolidinyl thiadiazolyl, oxadiazolyl, and tetrazolyl. In said "nitrogen containing 5-6 membered heterocyclic ring" 1 to 3 ring carbons may optionally bear (C_1-C_4)alkyl substituents defined as above. When a ring carbon is saturated it may be simultaneously substituted with two (C_1-C_4)alkyl groups.

When the above defined "nitrogen containing 5-6 membered heterocyclic ring" is a wholly saturated ring, this definition includes also those heterocyclic rings which have two ring members bridged by an alkylene chain of 1 to 3 carbon atoms wherein a methylene group may optionally be replaced by a group -NH-or -N[(C_1-C_4)alkyl]. Examples of said bridged rings are the following:

1-azabicyclo[2.2.2]octane, 1,4-diazabicyclo[3.2.2]-nonane, 1-azabicyclo[2.2.1]heptane, 1-azabicyclo-[3.2.1]octane, 8-azabicyclo[3.2.1]octane, 3-azabicyclo[3,2,1]octane, 1-azabicyclo[3.3.1]nonane, 9-azabicyclo[3.3.1]nonane, 3,8-diazabicyclo[3,2,1]-octane, 2-azabicyclo[2,2,1]heptane, 2-azabicyclo-[2.2.2]octane, 3-azabicyclo[3.2.2]nonane.

Accordingly, representative compounds of this invention include those of the general formula above where the symbol



represents a substituent derived from one of the following moieties:

1-azabicyclo[2.2.2]octan-3-amine,

1-azabicyclo[2.2.2]octan-2-amine,

1-azabicyclo[2.2.2]octan-3-amine, 6-methyl

1-azabicyclo[2.2.2]octan-3-amine, N-methyl

1-azabicyclo[2.2.2]octan-3-ethanamine,

1-azabicyclo[2.2.2]octan-4-amine,

1-azabicyclo[2.2.2]octan-4-amine, N-methyl

1-azabicyclo[2.2.2]octan-2-methanamine,

1-azabicyclo[2.2.1]heptan-3-amine

1-azabicyclo[3.2.1]octan-3-methanamine,

8-azabicyclo[3.2.1]octan-3-amine, 8-methyl

8-azabicyclo[3.2.1]octan-3-amine, 8-ethyl

8-azabicyclo[3.2.1]octan-2-methanamine,

3-azabicyclo[3.2.1]octan-3-ethanamine,

1-azabicyclo[3.3.1]nonan-4-amine

1-azabicyclo[3.3.1]nonan-3-methanamine

9-azabicyclo[3.3.1]nonan-3-amine, 9 methyl

2-azabicyclo[2.2.1]heptan-5-amine, 2-methyl

2-azabicyclo[2.2.2]octan-5-amine, 2-methyl

The expression "a saturated 5-7 membered heterocyclic ring which may optionally bear one to two (C_1-C_4)alkyl substituents on the ring carbons and may optionally contain a further heterogroup selected from -O-, -S-and -NR^3-" include, for instance, the following heterocyclic groups: morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, pyrazolidinyl, 1,3-oxazolidinyl, 1,3-thiazolidinyl and hexahydroazepinyl, which may optionally be substituted by one or two (C_1-C_4)alkyl group on the carbon skeleton.

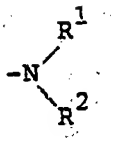
A preferred group of compounds of the invention is represents a hydrogen atom and the other substituents are as defined above.

A further preferred group of compounds of the invention are those compounds of formula I wherein R and R^1 represent hydrogen and the other substituents are as above defined.

A further preferred group of compounds of the invention is represented by those compounds of formula I wherein

R represents hydrogen

Y represents a group



wherein

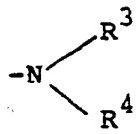
R^1 represents hydrogen, C_1-C_6)alkyl,

R^2 represents (C_1-C_6)alkyl, a nitrogen containing 5-6 membered heterocyclic ring which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents and one of the ring nitrogens may optionally bear a substituent R^6 selected from (C_1-C_4)alkyl, (C_4-C_7)-cycloalkyl, phenyl, and pyridyl;

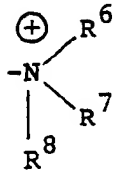
a wholly saturated nitrogen containing 5-6 membered heterocyclic ring which may contain a further

N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of th ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members ar bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N[(C_1-C_4)-alkyl];

a group -alk-W wherein "alk" represents a linear alkylene chain of 1 to 8 carbon atoms which is optionally substituted with a substituent selected from (C_1-C_4)alkyl, carbboxy, aminocarbonyl, (C_1-C_4)-alkylaminocarbonyl, di(C_1-C_4)alkylaminocarbonyl, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, and W represents a carboxy, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, aminocarbonyl, (C_1-C_4)aminocarbonyl, di(C_1-C_4)aminocarbonyl, glucosaminocarbonyl, ureido, guanidino, a nitrogen containing 5-6 membered heterocyclic ring which may be unsaturated, partially saturated or wh lly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents and one of the ring nitrogens may optionally bear a substituent R^5 selected from (C_1-C_4)alkyl, (C_4-C_7)cycloalkyl, phenyl, and pyridyl; a wholly saturated nitrogen containing 5-6 membered heterocyclic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N[(C_1-C_4)-alkyl]; a group of the formula



wherein R^3 and R^4 each independently represent hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl and halogeno(C_2-C_4)alkyl, or R^4 represents phenylmethyloxycarbonyl and R^3 represents hydrogen; a group of the formula



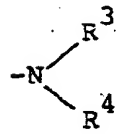
wherein R^6, R^7 and R^8 each independently represent a (C_1-C_4)alkyl,

or R^1 and R^2 taken together with the adjacent nitrogen atom represent a saturated 5-7 membered heterocyclic ring which may optionally bear one to two (C_1-C_4)alkyl substituents on the ring carbons and may contain a further heterogroup selected from -O-, -S-, and -NR^5-wherein R^5 is defined as above;

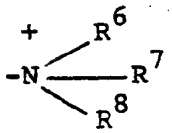
A represents hydrogen or -N[(C_{10}-C_{11})-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl,

B represents hydrogen or B-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl; with the proviso that B represents hydrogen only when A and M are simultaneously hydrogen and M represents hydrogen only when A is hydrogen and with the further proviso that when W represents a group



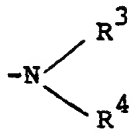
, a group



, ureido, guanidino or a nitrogen containing 5-6 membered heterocyclic ring as defined above directly connected with the "alk" moiety through a bond with a ring nitrogen atom, the linear alkylene "alk" moiety must be of at least two carbon atoms;

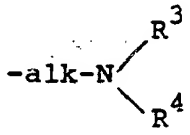
and the addition salts thereof.

A further preferred group of compounds of the invention includes those compounds of formula I wherein R, R¹ represent hydrogen and R² represents a group -alk-W wherein "alk" is a linear alkylene chain of 2 to 8 carbon atoms, W represent pyrrolidino, morpholino, thiomorpholino, piperidino or a piperazino optionally substituted on the N'nitrogen atom with a (C_1-C_6)alkyl, (C_4-C_7)cycloalkyl, benzyl, pyridinyl, or (C_1-C_4)alkylpyridinio group or W represents a group of the formula



wherein R^3 and R^4 each independently represent a (C_1-C_6)alkyl group and A, B and M are the same as above and the acid addition salts thereof.

Also preferred compounds of the invention are represented by those compounds of formula I wherein R, R¹, A, B and M represent hydrogen atoms and R² represents a group



wherein "alk" is a linear alkylene chain of 2 to 6 carbon atoms and R^3 and R^4 represent (C_1-C_6)alkyl groups and the pharmaceutically acceptable addition salts thereof.

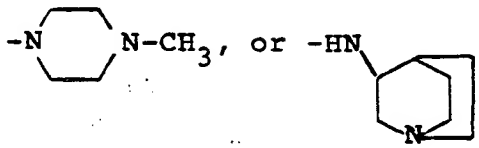
Another group of preferred compounds of the invention are those compounds of formula I wherein R represents hydrogen; R¹ represents hydrogen or (C_1-C_4)alkyl, R² represents a wholly saturated nitrogen containing 5-6 membered heterocyclic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N [(C_1-C_4)-alkyl];

or a group -alk-W wherein alk represents a linear alkylene chain of 1 to 3 carbon atoms and W is a wholly saturated nitrogen containing 5-6 membered heterocyclic ring defined as in the paragraph immediately above.

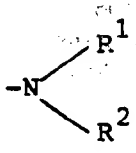
Another group of preferred compounds of the invention is represented by those compounds

wherein A, B, and M either r presents the sugar moieties as abov defined or each simultaneously represents a hydrogen atom.

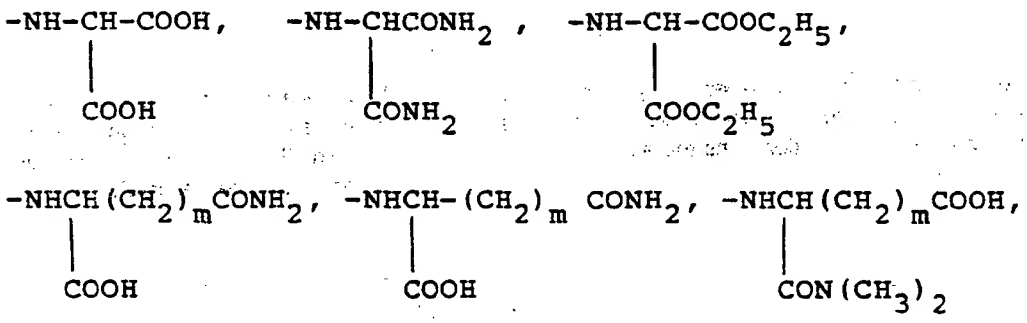
Other most preferred compounds are those of formula I wherein A, B and M either simultaneously represent the sugar moieties defined above or each simultaneously represent a hydrogen atom, R represents hydrogen, and NR^1R^2 represents a group -HN-(alk)W wherein "alk" repr sents a linear alkylene chain of 2, 3; 4, 5, 6, 7 or 8 units and W represents a group selected from: $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, and $-N(CH_3)(C_2H_5)$, or a group $-HNCH(COOCH_3)(CH_2)_4NH_2$,



Representative examples of the compounds of the invention include those compounds of formula I wherein R is hydrogen, A, B, and M are as defined above and



represents: $-NH_2$, $-NHC_4H_9$, $-NH(CH_2)_4-OH$, $-NHCH_2COOH$, $-NHCH_2COOCH_2C_6H_5$, $-NHCH_2COOC_2H_5$, $-NH-CH_2CONH_2$, $-NH-CH_2-CON(C_2H_5)_2$,



wherein m represents the integer 1, 2, 3 or 4, $-NH(CH_2)_n-NH_2$, $-NH-(CH_2)_nNHCH_3$, $-NH(CH_2)_n-N(CH_3)_2$, $-NH-(CH_2)_n N(C_2H_5)$, $-HN(CH_2)_nN(CH_3)(C_2H_5)$

wherein n represents 2, 3, 4, 5, 6, 7 or 8

$-NH-(CH_2)_2N(C_2H_4OH)(C_2H_4Cl)$;

$-NH(CH_2)_2N[(CH_2)_4OH]_2$, $-NH(CH_2)_4N(C_2H_4Cl)_2$, $-NH-(CH_2)_2N(C_4H_9)_2$, $-NH-(CH_2)_2\overset{\oplus}{N}(CH_3)_3$

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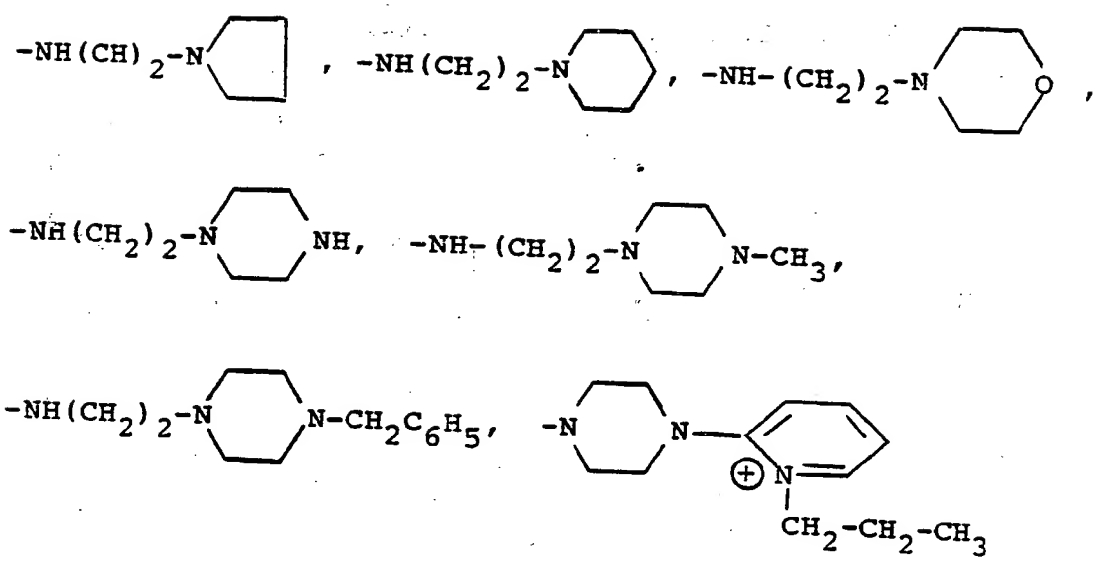

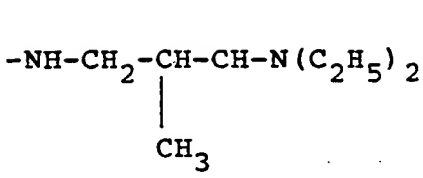

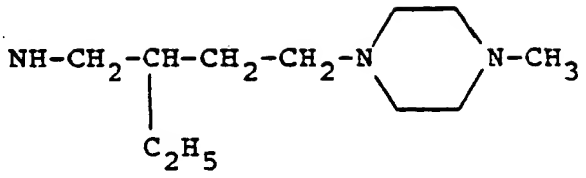

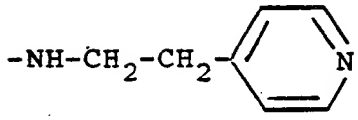

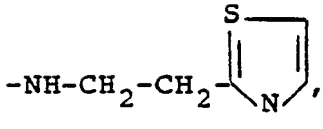

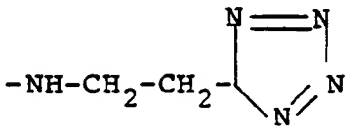

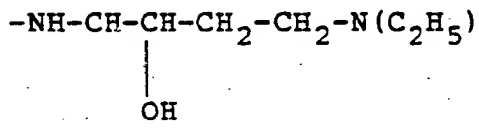

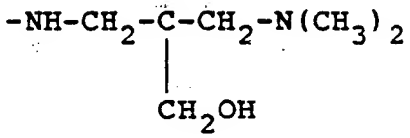

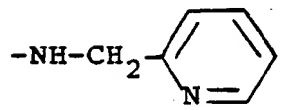

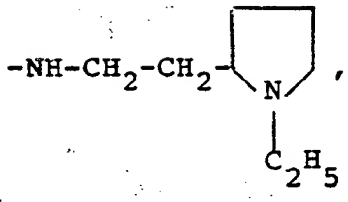

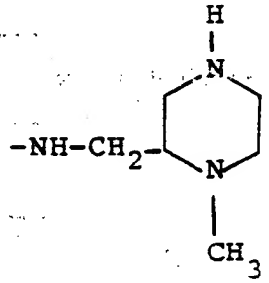

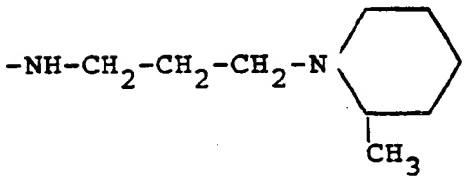

$-N(CH_3)_2$, $N(CH_2CH_2OH)_2$, $-N(CH_2CH_2NH_2)_2$, $-N(CH_2CH_2NHCH_3)_2$,

$-N[CH_2CH_2N(CH_3)_2]_2$, $-N(CH_3)(CH_2CH_2NH_2)$, $-N(CH_3)[-(CH_2)NHCH_3]$, $-N(CH_3)[CH_2)_2N(CH_3)_2]$, $-N(C_2H_5)[-(CH_2)_2-NHCH_3]$, $-N[CH_2CH_2CH_2N(C_2H_5)_2]_2$,

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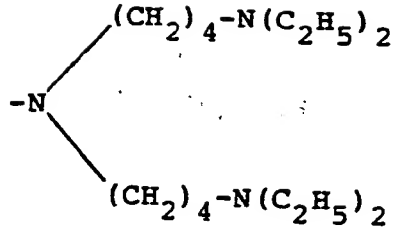
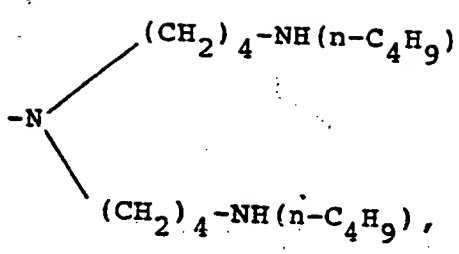
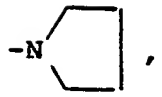
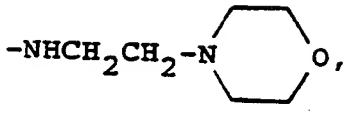
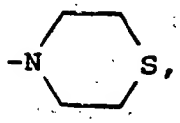
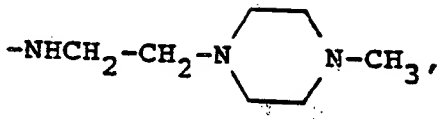


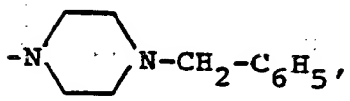


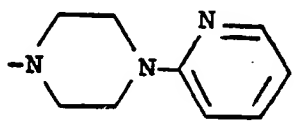


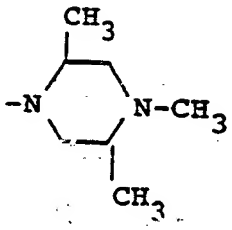


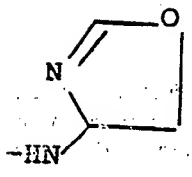


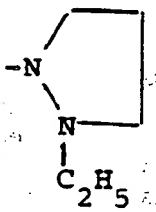


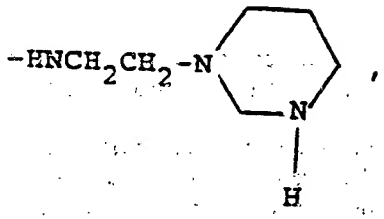


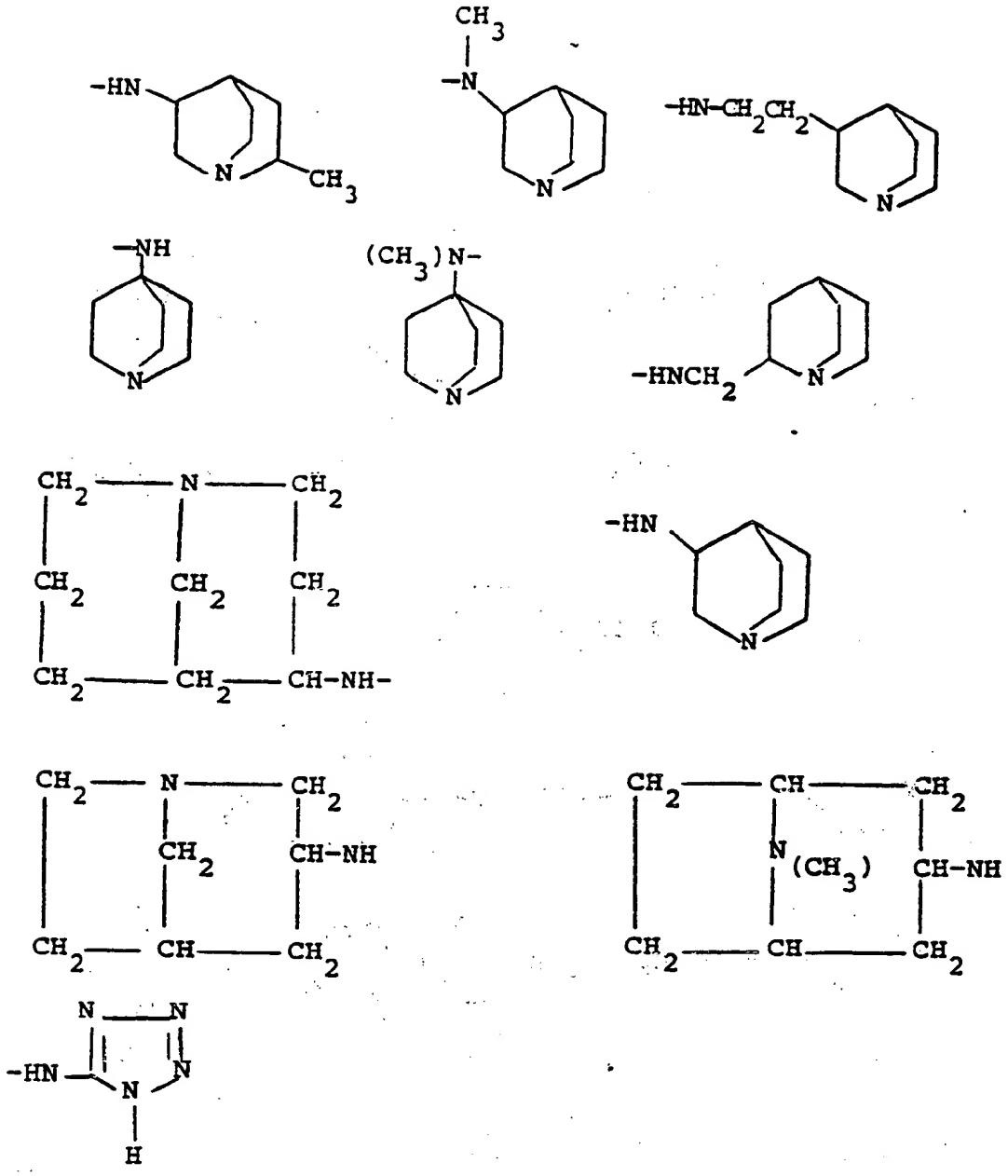












The compounds of the invention can form salts according to conventional procedures.

In particular, those compounds of formula I wherein R represent hydrogen as well as those compounds of formula I wherein the group $-NR^1R^2$ contains further amine functions form acid addition salts.

In addition, those compounds of the invention which contain acid functions in the $-NR^1R^2$ moiety may also form base addition salts.

In general, those compounds of the invention which contain acid and basic functions can form internal salts. For the scope of the present invention the "internal salts" are encompassed by the definition of the "non-salt" form. Preferred addition salts of the compounds of this invention are the pharmaceutically acceptable acid and/or base addition salts.

With the term "pharmaceutically acceptable acid and/or base addition salts" are intended those salts with acids and/or bases which from biological, manufacturing and formulation standpoint are compatible with the pharmaceutical practice as well as with the use in the animal growth promotion.

Representative and suitable acid addition salts of the compounds of formula I include those salts formed by standard reaction with both organic and

inorganic acids such as, for example, hydrochloric, hydrobromic, sulfuric, phosphoric, acetic, trifluoroacetic, trichloroacetic, succinic, citric, ascorbic, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, glutamic, camphoric, glutaric, glycolic, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic and the like acids. Representative examples of these bases are: alkali metal or alkaline-earth metal hydroxide such sodium, potassium, and calcium hydroxide; ammonia and organic aliphatic, alicyclic or aromatic amines such as methylamine, dimethylamine, trimethylamine, and picoline. When the compounds of the invention contain a (C_1-C_4)alkylpyridinio or a - $\overset{\oplus}{N}R^6R^7R^8$ moiety where R^6, R^7 and R^8 have the same meanings as above, the respective anion is an anion derived from a pharmaceutically acceptable acid. Representative examples of said anion are those deriving from the acids listed above.

The transformation of the free amino or non-salt compounds of the invention into the corresponding addition salts, and the reverse, i.e. the transformation of an addition salt of a compound of the invention into the non-salt or free amino from, are within the ordinary technical skill and are encompassed by the present invention.

For instance, a compound of formula I can be transformed into the corresponding acid or base addition-salt by dissolving the non-salt form in an aqueous solvent and adding a slight molar excess of the selected acid or base. The resulting solution or suspension is then lyophilized to recover the desired salt. Instead of lyophilizing, in some instances, it is possible to recover the final salt by extraction with an organic solvent, concentration to a small volume of the separated organic phase and precipitation by adding a non-solvent.

In case the final salt is unsoluble in an organic solvent where the non-salt form is soluble it is recovered by filtration from the organic solution of the non-salt form after addition of the stoichiometric amount or a slight molar excess of the selected acid or base.

The non-salt from can be prepared from a corresponding acid or base salt dissolved in an aqueous solvent which is then neutralized to free the non-salt form. This is then recovered for instance by extraction with an organic solvent or is transformed into another base or acid addition salt by adding the selected acid or base and working up as above.

When following the neutralization desalting is necessary, a common desalting procedure may be employed.

For example, column chromatography on controlled pore polydextrane resins (such as Sephadex L H 20) or silanized silica gel may be conveniently used. After eluting the undesired salts with an aqueous solution, the desired product is eluted by means of linear gradient or step-gradient of a mixture of water and a polar or apolar organic solvent, such as acetonitrile/water from 50:50 to about 100% acetonitrile.

As is known in the art, the salt formation either with pharmaceutically acceptable acids (bases) or non-pharmaceutically acceptable acids (bases) may be used as a convenient purification technique. After formation and isolation, the salt form of a compound of formula I can be transformed into the corresponding non-salt or into a pharmaceutically acceptable salt.

In some instances the acid addition salt of a compound of formula I is more soluble in water and hydrophilic solvents and has an increased chemical stability.

However, in view of the similarity of the properties of the compounds of formula I and their salts, what is said in the present application when dealing with the biological activities of the compounds of formula I applies also to their pharmaceutically acceptable salts, and viceversa.

The compounds of the invention are useful as semi-synthetic antibacterial agents mainly active against gram positive bacteria, but also active against gram negative bacteria.

The compounds of the invention wherein R is different from hydrogen while possessing a certain antimicrobial activity are mainly useful as intermediates for those compounds of formula I wherein R is hydrogen.

A general procedure for preparing a compound of the invention is represented by the reaction - (amidation) of a suitable teicoplanin starting material as above defined with the selected amine of formula HNR^1R^2 wherein R^1 and R^2 have the same meanings as above in an inert organic solvent in the presence of a condensing agent. When teicoplanin or teicoplanin A_2 complex is used as the starting material, the relative amide of formula I obtained according to the amidation reaction of this invention is a mixture of five amide derivatives corresponding to the five main components of teicoplanin A_2 as mentioned above. Said mixture may be separated into the five singl amide derivatives according to the techniques analogously known in the art (see for instance British Patent Application Publication No. 2121401). For clarity, both the mixture itself as obtained from the amida-

tion reaction and each of the five derivatives are intended to form part of this invention as claimed here with the meaning of A representing -N[(C_{10}-C_{11})aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl. Conversely, the single pure amide derivatives of each teicoplanin A_2 component is obtained by following the process of the invention starting from the single component itself instead of starting from the complex.

In carrying out the amidation for preparing the compounds of this invention, sometimes, and especially when at least one of A, B, and M in the teicoplanin starting material represent hydrogen, it is convenient to protect the primary amino function of the teicoplanin starting material in order to reduce possible undesired side-reactions.

Also, when the amine HNR^1R^2 contains further reactive functions such as amino or carboxy groups, which may unfavorably interfere with the course of the amidation they are protected by methods known per se in the art such as those described in reference books like T.W. Greene, "Protective Groups in Organic Synthesis", John Wiley and Sons, New York, 1981, and M. Mc. Omie "Protecting Groups in Organic Chemistry" Plenum Press, New York, 1973. These protecting groups must be stable at the conditions of the reaction process, must not unfavorably interfere with the main amidation reaction, and must be easily cleavable and removable from the reaction medium at the end of the reaction without altering the newly formed amide bond.

Representative examples of N-protecting groups which may be advantageously used in the process of the invention for protecting an amino function both in the teicoplanin starting material and, when appropriate, in the R^1 and R^2 moiety of the amine HNR^1R^2 are carbamate forming reagents characterized by the following oxycarbonyl groups:

1,1-dimethylpropynyloxycarbonyl, t-butyloxycarbonyl, vinyloxycarbonyl, aryloxycarbonyl, cinnamyloxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl-3, 4-dimethoxy-6-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 5-benzisoxanzolylmethyloxycarbonyl, 9-anthranylmethyloxycarbonyl, diphenylmethyloxycarbonyl, isonicotinyloxycarbonyl, diphenylmethyloxycarbonyl, isonicotinyloxycarbonyl, S-benzyloxycarbonyl, and the like.

Other suitable N-protecting agents are aldehydes or ketones, or derivatives thereof which are capable of forming Schiff bases with the amino group of the teicoplanin nucleus to be protected.

Preferred examples of such Schiff base forming agents are benzaldehydes and particularly preferred is 2-hydroxybenzaldahyde (salicylaldehyde).

A convenient means of protection in the case the amine reactant HNR^1R^2 contains a primary amino function as substituent for R^1 and/or R^2, is, in som instances, the formation of a benzyliden derivative which may be prepared by reacting th amine HNR^1R^2 with benzaldehyde in a lower alkanol, such as ethanol, preferably at room temperature. After the reaction with the selected teicoplanin starting material has been completed, the benzylidene protecting group may be removed has known in the art, e.g. by treating with diluted mineral acid, preferably hydrochloric acid, at room temperature.

Obviously, when the final compound of formula I contains groups which are labile under acidic conditions, e.g. when A, B or M represent sugar moieties as above defined which may be hydrolized in an acidic medium, other removal conditions must be use, such as catalytic hydrogenation using for instance Palladium on carbon as the catalyst to remove the proper protecting group.

In this case, however, attention should be paid to the presence of groups which may be modified by catalytic hydrogenation. A typical consequence of the catalytic hydrogenation of a derivative of formula I wherein A represents a group as above defined whose acyl portion is Z-decenoyl (i.e. a teicoplanin A_2 component 1 derivative or a mixture containing it) is that it is at least partially transformed into the corresponding decanoyl derivative (i.e. a derivative of teicoplanin A_2 component 3).

The man skilled in the art is capable, also on the basis of the present disclosure, of deciding which functions of the amine HNR^1R^2 need to be protected, how they must be protected and the proper deprotection reaction which is necessary to free the final compound.

For instance, a suitable protection for reactive carboxylic acid function is by forming an ester function.

As it is appreciated by the skilled technician, the ultimate choice of the specific protecting group depends on the characteristics of the particular amide derivative which is desired. In fact, this amide function of the removal of the protecting group(s).

Since the conditions of removal of the different protecting groups are known, the skilled technician is capable of selecting the proper protecting group. For instance, where the final compound posses also a benzyl ester function or N-benzyl function

the protecting groups which are usually removable by catalytic hydrogenation, such as the benzyloxycarbonyl group, should be avoided, while those protecting groups which are removable under acidic conditions, such as t.butoxycarbonyl, can be conveniently used. On the contrary, catalytic hydrogenation may be conveniently used in a case like the above when it is desired to convert a compound of formula I containing said N-benzyl or benzyl ester function in the -NR^1R^2 moiety into the corresponding compound wherein said N-benzyl or benzyl ester function is replaced by a hydrogen atom.

Inert organic solvents useful for the condensation reaction are those organic aprotic solvents which do not unfavorably interfere with the reaction course and are capable of at least partially solubilizing the teicoplanin starting material.

Examples of said inert organic solvents are organic amides, alkyl ethers, ethers of glycols and polyols, phosphoramides, sulfoxides and aromatic compounds. Preferred examples of inert organic solvents are: dimethylformamide, dimethoxyethane, hexamethylphosphoramide, dimethylsulfoxide, benzene, toluene and mixtures thereof.

The condensing agent in the process of the invention is one suitable for forming amide bonds in organic compounds and in particular in peptide synthesis.

Representative and preferred examples of condensing agents are (C_1-C_4)alkyl, phenyl or heterocyclic phosphorazidates such as, diphenyl phosphorazidate (DPPA), diethyl phosphorazidate, di-(4-nitrophenyl)phosphorazidate, dimorpholylphosphorazidate and diphenylphosphorochloridate. The preferred condensing agent is diphenyl phosphorazidate (DPPA).

In the process of the invention, the amine reactant HNR^1R^2 is normally used in a molar excess.

In general, a 2-to 6-fold molar excess is used while a 3-to 4-fold molar excess is preferred.

For the amidation to proceed, it is necessary that the amine HNR^1R^2 be capable of forming a salt with the carboxy function of the teicoplanin starting material. In case the amine HNR^1R^2 is not strong enough to form such a salt in the selected reaction medium, it is necessary to add a salt-forming base to the reaction mixture at least in an equimolecular amount with the teicoplanin starting material.

Examples of said salt-forming bases are tertiary organic aliphatic or alicyclic amines such as trimethylamine, triethylamine, N-methyl pyrrolidine or heterocyclic bases such as picoline, and the like.

The condensing agent is generally employed in a slight molar excess such as from 1.2 to 1.7 and preferably is 1.5 times th teicoplanin starting compound.

In addition, the amine reactant HNR^1R^2 may also conveniently be introduced in the reaction medium as a corresponding acid addition salt, e.g. the hydrochloride. In this case, at least a double molar proportion and preferably a 2 to 4 fold molar excess of a strong base capable of freeing the HNR^1R^2 amine from its salts, is used. Also in this case, the suitable base is a tertiary organic aliphatic or alicyclic amine like those exemplified above. In fact, at least in some instances, the use of salt of the amine HNR^1R^2, which is then freed in situwith the above memtiioned bases, is greatly preferred especially when the salt is more stable than the corresponding free amine.

The reaction temperature will vary considerably depending on the specific starting materials and reaction conditions. In general, it is preferred to conduct the reaction at temperatures between 0-20°C.

Also the reaction time vary considerably depending on the other reaction parameters. In general the condensation reaction is completed in about 24-48 h.

In any case, the reaction course is monitored by TLC or preferably by HPLC according to methods known in the art. On the basis of the results of these assays a man skilled in the art will be able to evaluate the reaction course and decide when to stop the reaction and start working up the reaction mass according to known per se techniques which include for instance extraction with solvents, precipitation by addition of non-solvents, etc., in conjunction with further separations and purifications by column chromatography.

As already said, when protection of the HNR^1R^2 reactant or of the teicoplanin starting material, or of both of them, is necessary, the protected final compound is then de-protected according to procedures which are known per se and mainly depends on the protecting group involved. In case both the amine HNR^1R^2 and the teicoplanin starting material are protected, it might be convenient to use a similar type of protection which may be removed under the same conditions, so that only one de-protection step is needed to free both functions.

It is also evident that in many instances a compound of the invention may be prepared in more than one way and that a compound of the

invention may be transformed into another by means of known per se reactions.

For instance, when the HNR^1R^2 amine is a diamine compound such as $HN(R^1)$-alk-NR^3R^4 defined above, the desired amine compound of formula I may be prepared either directly by condensing said amine, conveniently protected if necessary, with the selecting starting material or it can be prepared by reacting amide of formula I wherein the substituent R^2 is alk-halo, wherein halo is preferably a chlorine or bromine atom with an amine of formula HNR^3R^4. Moreover, an amide compound of formula I, bearing a carboxy function on the $-NR^1R^2$ moiety may be transformed into the corresponding amide or substituted amide derivative by usual techniques.

Moreover, said carboxy function may also be transformed into the corresponding ester of acyl halide function by usual techniques. More particularly, an ester function is in general formed by reacting the carboxy containing product with a preparation of an alcohol in the presence of an acid catalyst at a temperature varying between room temperature and the boiling point of the reaction mixture. The acid is preferably a mineral acid and the alcohol contains the moiety that is to be linked to the carboxylic function in the ester derivative. An inert solvent may also be used. Obviously, a compound of formula I bearing a carboxylic ester function on the $-NR^1R^2$ substituent may be transformed into the corresponding carboxylic compound by hydrolysis.

A preferred hydrolysis technique involves an aqueous solution of an alkali metal carbonate, like sodium or potassium carbonate, at a temperature from room temperature to the boiling point of the reaction mixture. A compound of formula I bearing an $-NH_2$ function on the $-NHR^2$ moiety may be transformed into the corresponding monoalylamino derivative by means of a "reductive alkylation" which involves reacting it with the selected carbonyl derivative (which is capable of giving the desired alkyl substituent upon reduction) to form the corresponding Schiff base intermediate which is then reduced in the presence of a suitable reducing agent such as sodium or potassium borohydride.

When a free amino group is present in the $-NR^1R^2$ moiety of formula I, it may be alkylated as known in the art, e.g. by reacting it, or possibly the corresponding compound wherein the primary amino group of the teicoplanin moiety has been protected, with an alkyl halide (bromide, chloride or iodide). Likewise, a secondary amino function may be transformed into a tertiary one or a tertiary amino function may be quaternized.

In addition, the sugar moiety of an amide compound of formula I may be selectively removed to transform it into another amide compound of formula I.

For example, an amide compound of formula I wherein A, B, and M represent a sugar moiety as above defined can be transformed into the corresponding compound wherein B and M are as above and A is hydrogen by means of controlled acid hydrolysis in a strong concentrated aqueous organic acid. The concentrated organic acid in this case is preferably aqueous trifluoroacetic acid at a concentration between 75% and 95%, and the reaction temperature is preferably between 10° and 50°C. The preferred hydrolysis conditions are represented by about 90% trifluoroacetic acid at room temperature. The reaction time varies depending on the other specific reaction parameters but, in any case, the reaction may be monitored by TLC or preferably HPLC techniques. An analogous selective hydrolysis is reported European Patent Application No 84114559.2.

Similarly, amide compounds of formula I wherein A, B, and M represent a sugar moiety as above defined or A represents hydrogen and B and M represent sugar moieties as above defined can be transformed into the corresponding amide compounds of formula I wherein A and M represent hydrogen and B represent a sugar moiety as defined by means of a selective hydrolysis with a strong acid in the presence of a polar aprotic solvent selected from ethers, ketones, and mixture thereof which are liquid at room termperature. Preferred hydrolysis conditions are in this case represented by the use of a concentrated mineral acid in the presence of an ether such as dimethoxyethane at room temperature. Also in this case, the reaction course may be monitored by TLC or preferably HPLC. An analogous selective hydrolysis is reported in European Patent Application No. 85109495.

According to another embodiment of the present invention, an amide compound of formula I wherein A, B and M represents sugar moieties as defined above, an amide compound of formula I wherein A represents hydrogen and B and M represent the above defined sugar moieties, or an amide compound of formula I wherein A and M represent hydrogen, and B represents a sugar moiety as above defined may be transformed into the corresponding amide compound of formula I wherein A, B and M represents hydrogen atoms by means of a selective hydrolysis in an organic protic solvent selected from aliphatic acids and alpha-halogenated aliphatic acids which at the reaction

temperature are liquids, aliphatic and cycloaliphatic alkanols which at the reaction temperature are liquids slightly mixable with wat r, phenylsubstituted lower alkanols wherein the phenyl moiety may optionally carry (C_1-C_4)alkyl, (C_1-C_4)alkoxy or halo rests which at the reaction temperature are liquids slightly mixable with water, and beta-polyhalogenated lower alkanols, which at the reaction temperature are liquids; in the presence of a strong acid, compatible with the solvent, selected from strong mineral acids, strong organic acids and strong acid cation exchange resins in the hydrogen form and at a temperature between 20°C and 100°C.

In this case, the preferred hydrolysis conditions are r presented by the use of a mineral acid, such as hydrochloric acid, in an haloalkanol such as trifluoroethanol, at a temperature between 65°C and 85°C.

Analogous selective hydrolysis conditions on a similar substrate are described in European Patent Application No. 84114558.4

In the following table (Table I) the structure formulas of representative examples of compounds of the invention are reported.

TABLE I

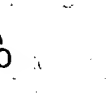
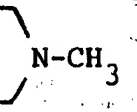
Compound	A	B	M	R	$-NR^1R^2$
1	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	H	$-NH(CH_2)_3N(CH_3)_2$
2a	do	do	do	do	$-NH(CH_2)_3N(C_2H_5)_2$
2b	$-GNHCOR_{(2)}$	do	do	do	do
3	$-GNHCOR_{(1-5)}$	do	do	do	$-NH(CH_2)_3N(n-C_4H_9)_2$
4	do	do	do	do	$-NH(CH_2)_2-N$ 
5	do	do	do	do	$-NH(CH_2)_2-N$ 
6	do	do	do	do	$-N$  $N-CH_3$

TABLE I (continued)

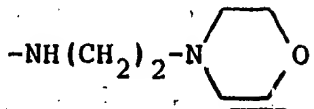
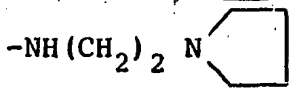
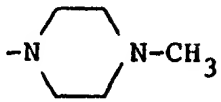
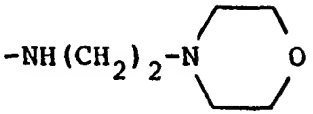
Compound	A	B	M	R	$-NR^1R^2$
7	H	$-GNHCOCH_3$	-M	H	$-NH(CH_2)_3N(CH_3)_2$
8	do	do	do	do	$-NH(CH_2)_3N(C_2H_5)_2$
9	do	do	do	do	$-NH(CH_2)_3N(n\text{-}C_4H_9)_2$
10	do	do	do	do	
11	do	do	do	do	
12	do	do	do	do	
13	do	do	H	do	$-NH(CH_2)_3N(CH_3)_2$
14	do	do	do	do	

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
15	H	$-GNHCOCH_3$	H	H	$-NH(CH_2)_2-N$
16	do	do	do	do	$-NHCH_2COOC_2H_5$
17	do	do	do	do	$-NHCH_2COOCH_3$
18	do	H	do	do	$-NH(CH_2)_3N(CH_3)_2$
19	do	do	do	do	$-NH(CH_2)_3N(C_2H_5)_2$
20	do	do	do	do	$-NH(CH_2)_3N(n-C_4H_9)_2$
21	do	do	do	do	$-NH(CH_2)_2-N$ O
22	do	do	do	do	$-NH(CH_2)_2-N$

TABLE I (continued)

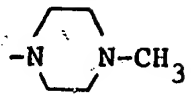
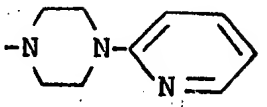
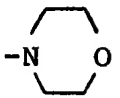
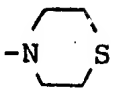
Compound	A	B	M	R	$-NR^1R^2$
23	H	H	H	H	
24	do	do	do	do	
25	do	do	do	do	
26	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	do	

TABLE I (continued)

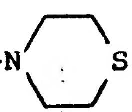
Compound	A	B	M	R	$-NR^1R^2$
27	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	H	$-NHCH(COOH)-(CH_2)_4NH_2$
28	H	do	do	do	-N 
29	do	do	do	do	$-NH-CH(COOH)-(CH_2)_4NH_2$
30	do	H	H	do	$-NH(CH_2)_2N(CH_2CH_2OH)(CH_2CH_2Cl)$

TABLE I (continued)

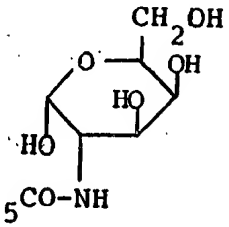
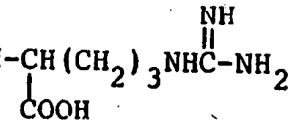
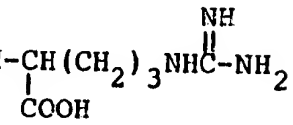
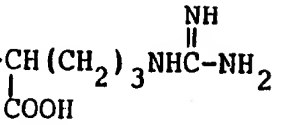
Compound	A	B	M	R	$-NR^1R^2$
31	H	H	H	H	
32a	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	do	
32b	$-GNHCOR_{(2,3)}$	do	do	do	
32c	$-GNHCOR_{(4,5)}$	do	do	do	

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
33	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	H	$-NH-\underset{\underset{COOCH_3}{\vert}}{CH}(CH_2)_3NH\overset{\overset{NH}{\Vert}}{C}-NH_2$
34	do	do	do	do	$-HN(CH_2)_3N(C_5H_{11})_2$
35	do	do	do	do	$-HN(CH_2)_3N(C_6H_{13})_2$
36	do	do	do	do	$-NH(CH_2)_4-\underset{\underset{COOH}{\vert}}{CH}NH_2$
37	do	do	do	do	$-NH(CH_2)_4\underset{\underset{COOCH_3}{\vert}}{CH}NH_2$
38	do	do	do	do	$-NHCH_2COOCH_3$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
39	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	H	$-NHCH(CH_2)_2COOH$ COOH
40	do	do	do	do	$-NHCH(CH_2)_2CONH_2$ COOH
41	H	do	do	do	$-NHCH(CH_2)_3NHC(=NH)-NH_2$ COOH
42	do	do	do	do	$-NHCH(CH_2)_3NHC(=NH)-NH_2$ $COOCH_3$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
43	H	$-GNHCOCH_3$	-M	H	$-NH(CH_2)_3N(C_5H_{11})_2$
44	do	do	do	do	$-NH(CH_2)_3N(C_6H_{13})_2$
45	do	do	do	do	$-NH(CH_2)_4-\underset{\displaystyle COOH}{\overset{\displaystyle CHNH_2}{|}}$
46	do	do	do	do	$-NH(CH_2)_4-\underset{\displaystyle COOCH_3}{\overset{\displaystyle CHNH_2}{|}}$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
47	H	$-GNHCOCH_3$	-M	H	$-NHCH_2COOCH_3$
48	do	do	do	do	$-NHCH(CH_2)_2COOH$ COOH
49	do	do	do	do	$-NHCH(CH_2)_2CONH_2$ COOH

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
50	H	$GNHCOCH_3$	H	H	$-NHCH(CH_2)_3NHC(=NH)-NH_2$ COOH
51	do	do	do	do	$-NHCH(CH_2)_4NH_2$ $COOC_2H_5$
52	do	do	do	do	$-HN(CH_2)_3N(C_5H_{11})_2$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
53	H	$GNHCOCH_3$	H	H	$-HN(CH_2)_3N(C_6H_{13})_2$
54	do	do	do	do	$-NH(CH_2)_4-\underset{\displaystyle COOCH_3}{\overset{\displaystyle CHNH_2}{\vert}}$
55	do	do	do	do	$-NH(CH_2)_4-\underset{\displaystyle COOH}{\overset{\displaystyle CHNH_2}{\vert}}$
56	do	do	do	do	$-NHCH_2COOH$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
57	H	$-GNHCOCH_3$	H	H	$-NHCH(CH_2)_2COOH$ COOH
58	do	do	do	do	$-NHCH(CH_2)_2CONH_2$ COOH
59	do	H	do	do	$-NHCH(CH_2)_3NHC(=NH)-NH_2$ COOH
60	do	do	do	do	$-NHCH(CH_2)_3NHC(=NH)-NH_2$ $COOCH_3$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
61	H	H	H	H	$-NH(CH_2)_3N(C_5H_{11})_2$
62	do	do	do	do	$-NH(CH_2)_3N(C_6H_{13})_2$
63	do	do	do	do	$-NH(CH_2)_4\underset{\displaystyle COOCH_3}{\overset{\displaystyle CHNH_2}{|}}$
64	do	do	do	do	$-NH(CH_2)_4\underset{\displaystyle COOH}{\overset{\displaystyle CHNH_2}{|}}$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
65	H	H	H	H	$-NHCH_2COOH$
66	do	do	do	do	$-NHCH(CH_2)_2COOH$ COOH
67	do	do	do	do	$-NHCH(CH_2)_2CONH_2$ COOH
68	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	H	$-NH-CH(CH_2)_4NHCOOCH_2-C_6H_5$ $COOCH_3$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
69	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	H	$-NH-\underset{\underset{COOH}{|}}{CH}(CH_2)_4NHCOOCH_2-C_6H_5$
70	do	do	do	do	$-N-\underset{\underset{CH_3}{|}}{(CH_2)_2}N(CH_3)_2$
71	$-GNHCOR_{(2,3)}$	do	do	do	$-NH-\underset{\underset{COOCH_3}{|}}{CH}(CH_2)_4NH_2$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
72	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	$COOCH_2-C_6H_5$	$-NH-\underset{\displaystyle COOCH_3}{\underset{\vert}{CH}}(CH_2)_4NHCOOCH_2-C_6H_5$
73	H	H	H	H	$-NH-\underset{\displaystyle COOCH_3}{\underset{\vert}{CH}}(CH_2)_4NH_2$
74	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	H	$-NH-\underset{\displaystyle COOCH_2-C_6H_5}{\underset{\vert}{CH}}-(CH_2)_3-NH-\overset{\displaystyle NH}{\overset{\Vert}{C}}-NH-NO_2$

TABLE I (continued)

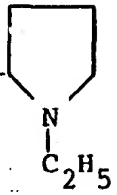
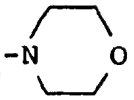
Compound	A	B	M	R	$-NR^1R^2$
75	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	-M	H	$-N(CH_3)_2$
76	do	do	do	do	
77	do	do	do	do	
78	H	H	H	H	

TABLE I (continued)

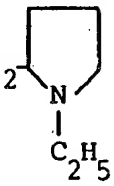
Compound	A	B	M	R	$-NR^1R^2$
79	H	H	H	H	
80	$-GNHCOR_{(1,5)}$	$-GNHCOCH_3$	-M	do	$-NH(CH_2)_6NH_2$
81	do	do	do	do	$-NH(CH_2)_4N(CH_3)_2$
81a	$-GNHCOR_{(2)}$	do	do	do	do

TABLE I (continued)

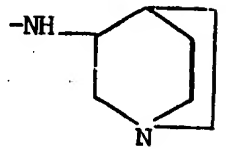
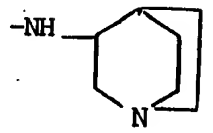
Compound	A	B	M	R	$-NR^1R^2$
82	$-GNHCOR_{(1,5)}$	$-GNHCOCH_3$	-M	H	
83	H	H	H	H	
84	do	do	do	do	$-NH-\underset{\underset{COOH}{|}}{CH}-(CH_2)_4-NH_2$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
85	$-GNHCOR_{(1,5)}$	$-GNHCOCH_3$	-M	H	$-NH-CH_2-COOC_2H_5$
86	do	do	do	do	$-NH-CH_2-COOH$
87	do	do	do	do	$-NH(CH_2)_5N(CH_3)_2$
88	do	do	do	do	$-NH(CH_2)_7N(CH_3)_2$
88a	$-GNHCOR_{(2)}$	do	do	do	do

TABLE I (continued)

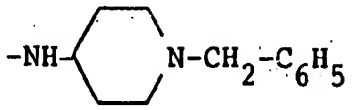
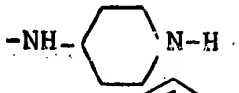
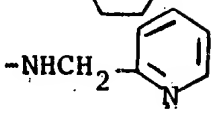
Compound	A	B	M	R	$-NR^1R^2$
89	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	M	H	
90	do	do	M	H	
91	do	do	do	do	
92	do	do	do	do	$-NHCH(CH_2)_3CH_3$ $COOCH_3$
93	H	H	H	H	$-N-(CH_2)_2N(CH_3)_2$ CH_3
94	do	do	do	do	$-NH(CH_2)_2N(CH_3)_2$
94a	$-GNHCOR_{(2)}$	do	do	do	do

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
95	$-GNHCOR_{(1-5)}$	$-GNHCOCH_3$	M	do	$-NH(CH_2)_2N(CH_3)_2$
96	do	do	do	do	$-NH(CH_2)_4NH_2$
97	H	H	H	H	$-NH(CH_2)_4N(CH_3)_2$
98	do	do	do	do	$-NH-CH(CH_2)_3NHC(=NH)-NH_2$ $COOCH_2C_6H_5$
99	do	do	do	do	$-NH(CH_2)_4NH_2$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
100	H	H	H	H	$-NH(CH_2)_5N(CH_3)_2$
101	do	do	do	do	$-NH(CH_2)_7N(CH_3)_2$
102	do	do	do	do	$-NH(CH_2)_6NH_2$
103	do	do	do	do	$-NH-\underset{\underset{COO-n-C_4H_9}{|}}{CH}(CH_2)_3NH\overset{\overset{NH}{||}}{C}-NH_2$

TABLE I (continued)

Compound	A	B	M	R	$-NR^1R^2$
104	$-GNHCOR_{(1,5)}$	$-GNHCOCH_3$	-M	do	$-NH-CH(CH_2)_3NHC(=NH)-NH-NO_2$ COOH
105	do	do	do	do	$-NH-CH(CH_2)_3NHC(=NH)-NH-NO_2$ $COOCH_3$

Note:

$-GNHCOR_{(1-5)}$ = N-[C_{10}-C_{11} aliphatic acyl]-β-D-2-deoxy-2-aminoglucopyranosyl

$-GNHCOR_{(2,3)}$ = N-(8-methylnonanoyl)-β-D-2-deoxy-2-aminoglucopyranosyl and N-decanoyl-β-D-2-deoxy-2-aminoglucopyranosyl

$-GNHCOR_{(4,5)}$ = N-(8-methyldecanoyl)-β-D-2-deoxy-2-aminoglucopyranosyl and N-(9-methyldecanoyl)-β-D-2-deoxy-2-aminoglucopyranosyl

$-GNHCOCH_3$ = N-acetyl-β-D-2-deoxy-2-aminoglucopyranosyl

-M = α-D-mannopyranosyl

The following table (Table II) lists the methods of preparation, startings material and reaction yields of representative examples of compounds of the inventi n:

TABLE II

Compound	Method of preparation	Starting material		Yield %
1	A_1	teicoplanin A_2	$H_2N(CH_2)_3N(CH_3)_2$	46
2a	A_1	teicoplanin A_2	$H_2N(CH_2)_3N(C_2H_5)_2$	50
2b	A_1	teicoplanin A_2, component 2	$H_2N(CH_2)_3N(C_2H_5)_2$	55
	G	compound 2a		46
3	A_1	teicoplanin A_2	$H_2N(CH_2)_3N(n\text{-}C_4H_9)_2$	42

TABLE II (continued)

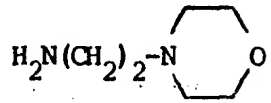
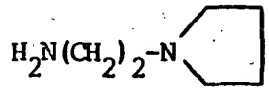
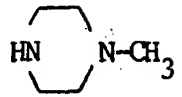
Compound	Method of preparation	Starting material		Yield %
4	A_1	teicoplanin A_2		66
5	A_1	teicoplanin A_2		61
6	A_1	teicoplanin A_2		47
7	C	compound 1		99

TABLE II (continued)

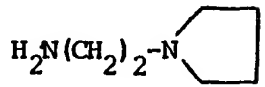
Compound	Method of preparation	Starting material		Yield %
8	C	Compound 2		96
9	C	Compound 3		98
	B_1	N-CBzO-antibiotic L 17054	$H_2N(CH_2)_3N(n\text{-}C_4H_9)_2$	46
10	C	Compound 4		95
11	C	Compound 5		96
	B_2	N-t-BOC-antibiotic L 17054		55
12	C	Compound 6		94

TABLE II (continued)

Compound	Method of preparation	Starting material		Yield %
13	A_2	Antibiotic L 17046	$H_2N(CH_2)_3N(CH_3)_2$	53
	B_1	N-CBzO-antibiotic L 17046	$H_2N(CH_2)_3N(CH_3)_2$	32
	D_1	Compound 1		83
	D_2	Compound 7		88
14	D_1	Compound 4		46
	B_2	N-t-BOC-antibiotic L 17046	$H_2N(CH_2)_2$-N⟨morpholine⟩O	48
15	D_1	Compound 11		67
16	A_3	Antibiotic L 17046	$H_2NCH_2COOC_2H_5$ (HCl)	53
17	F_1	Compound 16		78

TABLE II (continued)

Compound	Method of preparation	Starting material		Yield %
18	A_2	Deglucoteicoplanin	$H_2N(CH_2)_3N(CH_3)_2$	16
	B_2	N-t-BOC-deglucoteicoplanin	$H_2N(CH_2)_3N(CH_3)_2$	37
	E_1	Compound 1		61
	E_2	Compound 7		56
19	B_2	N-t-BOC-deglucoteicoplanin	$H_2N(CH_2)_3N(C_2H_5)_2$	51
	E_1	Compound 2		43
	E_2	Compound 8		46
20	B_2	N-t-BOC-deglucoteicoplanin	$H_2N(CH_2)_3N(n\text{-}C_4H_9)_2$	48
	E_1	Compound 3		56
	E_2	Compound 3		51

TABLE II (continued)

Compound	Method of preparation	Starting material		Yield %
21	B_2	N-t-BOC-deglucoteicoplanin	$H_2N(CH_2)$-N⟨ ⟩O	39
	E	Compound 4		37
	D*	Compound 4		65
	E	Compound 14		39
	D*	Compound 14		65
22	E	Compound 5		44
	B_1	N-CBzO-deglucoteicoplanin	$H_2N(CH_2)_2$-N⟨ ⟩	24
23	B_2	N-t-BOC-deglucoteicoplanin	HN⟨ ⟩N-CH_3	28
	E_2	Compound 12		39
24	B_2	N-t-BOC-deglucoteicoplanin	HN⟨ ⟩N-⟨ ⟩N	30

TABLE II (continued)

Compound	Method of preparation	Starting material	Yield %
25	B_2	N-t-BOC-deglucoteicoplanin	35
26	A_1	Teicoplanin A_2	62
27	A_4	Teicoplanin A_2	41
28	C	Compound 26	90
29	C	Compound 27	90
30	E_2	Compound 4	29

TABLE II (continued)

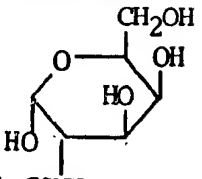
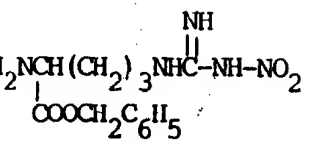
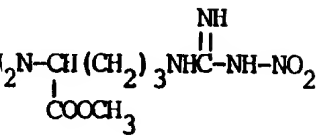
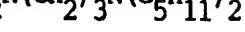
Compound	Method of preparation	Starting material	Yield %
31	B_2	t-BOC-degluco-teicoplanin		76
32a	A_7	Teicoplanin A_2		38
32b	G	Compound 32	64
32c	G	Compound 32	56
33	A_6	Teicoplanin A_2		64
34	A_1	Teicoplanin A_2		~ 50

TABLE II (continued)

Compound	Method of preparation	Starting material		Yield
35	A_1	Teicoplanin A_2	$H_2N(CH_2)_3N(C_6H_{13})_2$	~60
36	A_4	Teicoplanin A_2	$CBzO-NHCH(COOCH_2C_6H_5)(CH_2)_4NH_2$	~30
37	A_4	Teicoplanin A_2	$CBzO-NHCH(COOCH_3)(CH_2)_4NH_2$	~40
38	A_3	Teicoplanin A_2	$NH_2CH_2COOCH_3.HCl$	~45
39	A_4	Teicoplanin A_2	$H_2NCH(COO-CH_2-C_6H_5)(CH_2)_2COO$-t-butyl	~70
40	F_2	Teicoplanin A_2	$H_2NCH(COOCH_3)(CH_2)_2CONH_2$	~25

TABLE II (continued)

Compound	Method of preparation	Starting material	Yield %
41	C	Compound 32	~90
42	C	Compound 33	~90
43	C	Compound 34	~90
44	C	Compound 35	~90
45	C	Compound 36	~90
46	C	Compound 37	~90
47	C	Compound 38	~90
48	C	Compound 39	~90
	A_5	Antibiotic L 17054 $NH_2CH(CH_2)_2COOt\text{-butyl}$ (1-COOt-butyl)	~50
49	C	Compound 40	~90

TABLE II (continued)

Compound	Method of preparation	Starting material		Yield %
50	D_1	Compound 41		~30
51	F_3	Compound 27		30
52	B_2	t-BOC-antibiotic L 17046	$H_2N(CH_2)_3N(C_5H_{11})_2$	~55
53	B_2	t-BOC-antibiotic L 17046	$H_2N(CH_2)_3N(C_6H_{13})_2$	~60
54	B_1	CBzO-antibiotic L 17046	$CBzO-NHCH(CH_2)_4NH_2$ $\cdot COOCH_3$	~60
55	F_2	Compound 54		~50
56	B_3	t-BOC-antibiotic L 17046	NH_2CH_2COO-t-butyl	~90

TABLE II (continued)

Compound	Method of preparation	Starting material		Yield %
57	A_5	antibiotic L 17046	$NH_2CH(CH_2)_2COO\text{-t-butyl}$ $COO\text{-t-butyl}$	~30
	B_3	t-BOC-antibiotic L 17046	$NH_2CH(CH_2)_2COO\text{-t-butyl}$ $COO\text{-t-butyl}$	~60
58	B_3	t-BOC-antibiotic L 17046	$NH_2CH(CH_2)_2CONH_2$ $COO\text{-t-butyl}$	~70
59	B_1	CBzO-deglucoteicoplanin	$NH_2CH(CH_2)_3NHC(=NH)\text{-}NH_2\text{-}NO_2$ $COOCH_2C_6H_5$	~40
60	A_7	CBzO-deglucoteicoplanin	$NH_2CH(CH_2)_3NHC(=NH)\text{-}NH\text{-}NO_2$ $COOCH_3$	~70
61	B_1	CBzO-deglucoteicoplanin	$NH_2(CH_2)_3N(C_5H_{11})_2$	~65

TABLE II (continued)

Compound	Method of preparation	Starting material		Yield %
62	B_1	CB_zO-deglucoteicoplanin	$NH_2(CH_2)_3N(C_6H_{13})_2$	~ 40
63	B_3	CB_zO-deglucoteicoplanin	$CBzO-NHCH(COOCH_3)(CH_2)_4NH_2$	~ 60
64	F_2	Compound 63		84
65	B_2	t-BOC-deglucoteicoplanin	NH_2CH_2COO-t-butyl	~ 90
66	B_3	t-BOC-deglucoteicoplanin	$NH_2CH(COO\text{-t-butyl})(CH_2)_2COO$-t-butyl	87
67	B_2	t-BOC-deglucoteicoplanin	$NH_2CH(COO\text{-t-butyl})(CH_2)_2CONH_2$	~ 80

TABLE II (continued)

Compound	Method of preparation	Starting material	Yield %
68	B_3	teicoplanin A_2	$H_2NCH(COOCH_3)(CH_2)_4NHCOOCH_2CH_2C_6H_5$	87
69	F_2	compound 68	92
70	A_2	teicoplanin A_2	$HN(CH_3)(CH_2)_2N(CH_3)_2$	36
71	A_4	teicoplanin A_2	$H_2N-CH(COOCH_3)(CH_2)_4NHCOOCH_2C_6H_5$	63
72	B_3	CBzo-degluco-teicoplanin	$H_2N-CH(COOCH_3)(CH_2)_4NHCOOCH_2C_6H_5$	91
73	B_1	degluco-teicoplanin	$H_2N-CH(COOCH_3)(CH_2)_4NHCOOCH_2C_6H_5$	41

TABLE II (continued)

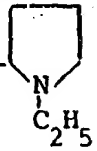
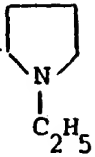
Compound	Method of preparation	Starting material		Yield %
74	B_3	teicoplanin A_2	$H_2N-CH(CH_2)_3-NHC(=NH)-NH-NO_2$ $COOCH_2C_6H_5$	64
75	A_3	teicoplanin A_2	$HN(CH_3)_2$ (.HCl)	90
76	A_2	teocoplanin A_2	H_2N-CH_2- 	67
77	A_2	teicoplanin A_2	$H_2N(CH_2)_3-N$ 	82
78	B_2	t-BOC-deglucoteicoplanin	$H_2N(CH_2)_3-N$ 	49
79	B_2	t-BOC-deglucoteicoplanin	H_2N-CH_2- 	53
80	A_2	teicoplanin A_2	$H_2N(CH_2)_6NH_2$	21
81	A_2	teicoplanin A_2	$H_2N(CH_2)_4N(CH_3)_2$	71

TABLE II (continued)

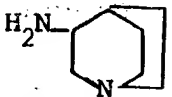
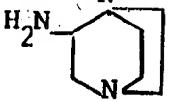
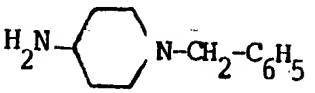
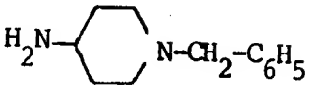
Compound	Method of preparation	Starting material	Yield %
82	A_1	teicoplanin A_2		84
83	B_2	t-BOC-deglucoteicoplanin		63
84	E_2	Compound 27	39
85	A_3	teicoplanin A_2	$H_2NCH_2COOC_2H_5$ (HCl)	83
86	F_2	Compound 85	91
87	A_1	teicoplanin A_2	$H_2N(CH_2)_5N(CH_3)_2$	66
88	A_1	teicoplanin A_2	$H_2N(CH_2)_7N(CH_3)_2$	58
89	A_2	Teicoplanin A_2		61
90	A_4	teicoplanin A_2		37

TABLE II (continued)

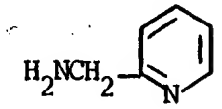
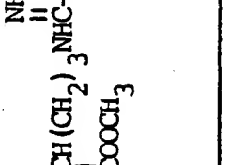
Compound	Method of preparation	Starting material		Yield %
91	A_2	teicoplanin A_2		26
92	A_3	teicoplanin A_2	$H_2N-CH(CH_2)_3CH_3$ (HCl) $COOCH_3$	74
93	A_2	teicoplanin A_2	$HN-(CH_3)_2N(CH_3)_2$	42
94	B_2	t-BOC-degluco-teicoplanin	$H_2N(CH_2)_2N(CH_3)_2$	39
95	A_1	teicoplanin A_2	$H_2N(CH_2)_2N(CH_3)_2$	48
96	A_2	teicoplanin A_2	$H_2N(CH_2)_4NH_2$	46

TABLE II (continued)

Compound	Method of preparation	Starting material	Yield %
97	E_1	Compound 81	71
98	A_7	t-BOC-degluco-teicoplanin + $H_2N-CH(COOCH_2C_6H_5)(CH_2)_3NHC(=NH)NHNO_2$	33
99	E_1	Compound 96	29
100	E_1	Compound 87	61
101	E_1	Compound 88	63
102	E_2	Compound 80	29
103	E_1	Compound 42	64

TABLE II (continued)

Compound	Method of preparation	Starting material	Yield %
104	F_2	Compound 105	86
105	A_3	teicoplanin A_2	85



HPLC Analysis

Th following table reports the R_t of representative examples of the compounds of the invention.

The assays were run with a VARIAN model 5000 LC pump equipped with a 20 µl loop injector. Rheodyne MOdel 7125 and a PERKIN-ELMER LC 15 UV detector at 254 µm.

Columns: pre-column (1.9 cm) Hibar LiChro Cart 25-4 MERCK pre-packed with LiChrosorb RP-8 -

(20-30 μm) followed by a column Hibar RT 250-4 MERCK pre-packed with LiChrosorb RP-8 (10 μm).

Eluents: A, 0.2% aq. $HCOONH_4$ and B, CH_3CN

Injection: 20 μl -Flow rate: 2 ml/min.

Th reaction is monitored by injecting, at established times, samples of the solutions (or suspensions) diluted with the solvent mixture (CH_3CN : H_2O, 6:4 (v/v) enough to obtain final concentrations of either 1, 2 or 3 mg/ml.

Method A : linear step gradient from 5 to 75% of B in A in 35 min according to the following program:

Time (min)	% B in A
0	5
10	23
20	30
30	50
35	75

Method B: linear gradient form 5 to 60% of B in A in 30 min.

Method C: linear gradient from 20 to 60% of B in A in 30 min.

Method D: suitable chromatographic conditions to compare all the teicoplanin amides with deglucoteicoplanin.

HPLC authomatic apparatus: Hewlett-Packard mod. 1084

Column: Hibar (Merck) LiChrosorb RP-8 (7μm)

Eluents: A, 0.02 M aq.NaH_2PO_4/CH_3CN 25/75 (v/v)

B, 0.02 M aq.NaH_2PO_4/CH_3CN 95/5 (v/v)

Elution: linear step gradient from 8 to 60% of B in A in 48 min., according to the following program:

Time (min)	% B in A
0	8
40	40
45	60
48	60

TABLE III

a) HPLC analysis of amides of teicoplanin A_2 (formula I wherein A is N-[(C_{10}-C_{11})aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl, B is N-acetyl-β-D-2-deoxy-2-aminoglucopyranosyl, M is α-D-mannopyranosyl) (Method A)

Compound	t_R (min)					k**
	1*	2*	3*	4*	5*	
1	22.9	23.6	23.9	25.3	25.5	1.475
2	23.4	24.2	24.5	25.8	26.1	1.512
3	26.4	27.0	27.3	28.2	28.4	1.687
4	19.6	20.6	21.2	22.9	23.2	1.287
5	23.6	24.1	24.4	25.6	25.9	1.506
6	20.3	21.2	21.7	23.5	23.7	1.325
26	21.1	22.2	22.7	24.2	24.4	1.387
27	-	17.3	17.6	18.8	19.0	1.081
teicoplanin A_2-2	15.1	16.0	16.4	18.1	18.5	1

* components of the teicoplanin A_2 complex

** k = relative retention time = $\frac{t_R \text{ amide}}{t_R \text{ teicoplanin } A_2, \text{ component 2}}$

b) HPLC analysis of amides of antibiotic L 17054 (formula I wherein A represents hydrogen, B is N-acetyl-β-D-2-deoxy-2-aminoglucopyranosyl, M is α-D-mannopyranosyl) (Method B)

Compound	t_R (min)	K
7	14.9	1.367
8	15.2	1.394
9	18.0	1.651
10	13.6	1.248
11	15.1	1.385
12	13.5	1.238
28	13.7	1.257
29	12.2	1.119
antibiotic L 17054	10.9	1

c) HPLC analysis of amides of antibiotic L 17046 (formula I wherein A and M represent hydrogen, B represents N-acetyl- β -D-2-deoxy-aminoglucopyranosyl) (Method B)

Compound	t_R (min)	K
13	16.7	1.403
14	15.1	1.269
15	17.6	1.479
16	17.61	1.479
17	14.6	1.227
antibiotic L 17046	11.9	1

d) HPLC analysis of amides of deglucoteicoplanin (formula I wherein A, B, and M represent hydrogen atoms) (Method C)

Compound	t_R (min)	K
18	19.2	1.524
19	20.3	1.611
20	25.2	2
21	16.4	1.302
22	20.6	1.635
23	17.2	1.365
24	19.1	1.516
25	16.3	1.294
30	22.9	1.817
31	14.5	1.150
deglucoteicoplanin	12.6	1

e) HPLC analysis according to method D
($K' = t_R/t_R$ of deglucoteicoplanin)

Compound	K'
(deglucoteicoplanin (t_R = 14.78 min.)	1.00)
(teicoplanin A_2	1.75)
1	2.09
2	2.16
3	2.60
4	2.13
5	2.15
6	2.06
7	0.85
8	0.89
9	1.45
10	0.85
11	0.88
12	0.86
13	1.00
14	1.03
15	1.05
16	1.18
17	1.05
18	1.32
19	1.48
20	2.48
21	1.36
22	1.44
23	1.38
24	1.99
25	1.49

Compound	K'
(deglucoteicoplanin (t_R = 14.78 min.)	1.00)
(teicoplanin A_2	1.75)
26	2.13
27	1.93
28	0.97
29	0.74
30	2.77
31	1.19
32	
33	
71	2.14
73	1.44
74	2.60
75	2.03
82	2.08
83	1.36
85	2.03
86	1.78
89	2.88
90	1.90
91	2.11
92	2.14
104	1.79
105	2.10

The K' values for the complex derivatives refer to the component 2

The following Table (Table IV) reports the acid-base titration data of some representative compounds of the invention. The assays were carried out in Methylcello-solve ®/H_2O, 4:1 (v/v). A sample - (10 µmole in about 20 ml) then 0.01 N HCl (2 ml) is added and the mixture is titrated with 0.01 in N KOH in the same solvent mixture.

TABLE IV

Acid base titration

Compound	Formula[1]	Salt form	MW[2]	EW	pK_1	pK_2	pK_3[3]
1		Acetate					
2		hydrochloride	1923	961.5	6.25	7.8	
3		do	2069.6	1034.8	6.3	8.0	
4		Acetate	1917	639	5.4	7.9	(6.8)
5		do	2071.8	690.6	5.9	8.5	(7.1)
6		acetate	2113.5	704.5	5.3	7.8	(6.6)
7	$C_{77}H_{80}Cl_2N_{10}O_{27}$	Di-trifluoro-acetate	2166	1083	6.4	7.9	
8	$C_{79}H_{84}Cl_2N_{10}O_{27}$	do					
9	$C_{83}H_{92}Cl_2N_{10}O_{27}$	do					
10	$C_{78}H_{80}Cl_2N_{10}O_{28}$	do	2076	1038	5.25	6.4	
11	$C_{78}H_{80}Cl_2N_{10}O_{27}$	do	1824	912	6.5	8.3	
12	$C_{77}H_{78}Cl_2N_{10}O_{27}$	do					
13	$C_{71}H_{70}Cl_2N_{10}O_{22}$	Di-hydrochloride					
14	$C_{72}H_{70}Cl_2N_{10}O_{23}$	do	1632	816	5.3	6.8	
15	$C_{72}H_{70}Cl_2N_{10}O_{22}$	do	1607.8	803.9	6.25	7.85	
16	$C_{70}H_{65}Cl_2N_9O_{24}$	Hydrochloride					

TABLE IV (continued)

Compound	Formula[1]	Salt form	MW[2]	EW	pK_1	pK_2	pK_3[3]
17	$C_{68}H_{61}Cl_2N_9O_{24}$	hydrochloride	1682.5	1682.5	6.4		
18	$C_{63}H_{57}Cl_2N_9O_{17}$	di-trifluoro-acetate					
19	$C_{65}H_{61}Cl_2N_9O_{17}$	hydrochloride	1260	630	6.30	8.0	
20	$C_{69}H_{69}Cl_2N_9O_{17}$	hydrochloride	1505.1	752.5	6.1	8.3	
21	$C_{64}H_{57}Cl_2N_9O_{18}$	di-trifluoro-acetate	1426	713	5.01	6.8	
22	$C_{64}H_{57}Cl_2N_9O_{17}$	do	1640	820	6.4	7.8	
23	$C_{63}H_{55}Cl_2N_9O_{17}$	do	1742.6	871.3	5.6	6.8	
24	$C_{67}H_{56}Cl_2N_{10}O_{17}$	acetate	1399	466.3	5.75	7.4	(6.6)
25	$C_{62}H_{52}Cl_2N_8O_{18}$	trifluoroacetate	1425	1425	6.6		
26		free base	2072	2072	6.7		
27		internal salt	2382.4	1191.2	6.8		
28		trifluoroacetate					
29		trifluoroacetate	2252	1126	6.75		4.8
30		trifluoroacetate	1462.4	731.2	5.4	6.9	
31		hydrochloride	1730	1730	6.45		

TABLE IV (continued)

Compound	Formula[1]	Salt form	MW[2]	EW	pK_1	pK_2	pK_3[3]
32a		di-hydrochloride			4.8	7.0	9.4
32b		hydrochloride			5.1	7.2	9.7
32c		di-hydrochloride			5.1	7.0	9.4
66		trifluoroacetate			4.8		
					6.1	7.2	
68		hydrochloride				6.5	
69		internal salt			4.9	7.2	
71		di-hydrochloride				6.5	8.9
73		di-hydrochloride				6.5	8.9
75		hydrochloride				6.6	

Notes to Table IV:

1) The molecular formula for the single components of the complex are as follows:

Teicoplanin A_2 component 1: 1877.7 for $C_{88}H_{95}Cl_2n_9O_{33}$
Teicoplanin A_2 component 2: 1879.7 for $C_{88}H_{97}Cl_2N_9O_{33}$
Teicoplanin A_2 component 3: 1879.7 for $C_{88}H_{97}Cl_2N_9O_{33}$
Teicoplanin A_2 component 4: 1893.7 for $C_{89}H_{99}Cl_2N_9O_{33}$
Teicoplanin A_2 component 5: 1893.7 for $C_{89}H_{99}Cl_2N_9O_{33}$

2) The difference between the found and theoretical value are due mainly to the presence of solvents (found value higher than theoretical value) or traces of excess of the acid used for salifying (found value lower than theoretical value).

3) The values between brackets are due to the titration of the carboxylic function of the salifying acid.

TABLE V: IR Data (cm^{-1}; nujol)

Compound	ν NH glycosidic and phenolic ν OH	νC=O (amide I)	δ NH (amide II)	glycosidic δOH, νC-O	phenolic ν C-O	ν COO^-	δ CF_3
1	3700-3100	1655	1510	1220-1180 1110-950	o.b.	1550	
2	3700-3100	1655	1510	1270-1180 1120-950	o.b.		
3	3700-3100	1655	1510	1270-1180 1120-950	o.b.		
4	3700-3100	1655	1510	1250-1180 1120-950	o.b.	1550	
5	3700-3100	1655	1510	1270-1180 1120-950	o.b.	1550	
6	3700-3100	1655	1510	1270-1190 1120-950	o.b.	1550	

Table V (continued)

Compound	νNH glycosidic and phenolic νOH	ν C=O (amide I)	δ NH (amide II)	glycosidic δOH, νC-O	phenolic ν C-O	ν COO^-	δ CF_3
7	3700-3100	1655	1515	1270,1190 1110-950	o.b.	-	1200,1135
8	3700-3100	1655	1515	1250-1160	o.b.	-	1200,1135
9	3700-3100	1650	1515	1270-1180 1100-950	o.b.	1665	1200,1140
10	3700-3100	1655	1515	1250-1180 1000-950	o.b.	-	1200,1140
11	3700-3100	1655	1515	1270-1180 1100-950	o.b.	1665	1200,1135
12	3700-3100	1655	1515	-	o.b.	1665	1200,1140

Table V (continued)

Compound	νNH glycosidic and phenolic ν OH	ν C=O (amide I)	δNH (amide II)	glycosidic δ OH, ν C-O	phenolic ν C-O	ν COO^-	δ CF_3
13	3700-3100	1655	1515	1230,1150 1100-990	o.b.	-	-
14							
15	3700-3100	1655	1515	1230,1140 1100-990	o.b.	-	-
16							
17	3700-3100	1655,1735 (ester)	1515	1250,1150 1100-990	o.b.		
18	3700-3100	1655	1515	-	1230,1200, 1080,1005	-	1200 1135

Table V (continued)

Compound	νNH glycosidic and phenolic ν OH	νC=O (amide I)	δNH (amide II)	glycosidic δ OH, ν C-O	phenolic ν C-O	ν COO^-	δ CF_3
19	3700-3100	1650	1515	-	1230,1200 1080,1005	- -	- -
20	3700-3100	1655	1515	-	1230,1200 1005	-	-
21	3700-3100	1655	1515	-	1230,1200, 1060,1005	1665	1200,1135
22	3700-3100	1655	1515	-	1200,1060 1010	1665	1200,1140
23	3700-3100	1655	1515	-	1230,1200 1060,1005	1665	1200,1135
24	3700-3100	1655	1515	-	1230,1200 1085,1005	1560	-

Table V (continued)

Compound	ν NH glycosidic and phenolic ν OH	ν C=O (amide I)	δ NH (amide II)	glycosidic δ OH, ν C-O	phenolic ν C-O	ν COO^-	δ CF_3
25	3700-3100	1655	1515	-	1230,1200 1060,1005	1660	1200,1135
26	3700-3100	1650	1515	1270-1180 1100-950	o.b.	-	-
27	3700-3100	1650	1510	1250-1200 1100-950	o.b.	-	-
28							
29	3700-3100	1655	1510	1250-1200 1100-950	o.b.	1660	1200,1135
30	3700-3100	1655	1515	-	-	1670	1200,1135
31	3700-3100	1650	1515	-	1230,1080 1010	-	-

Table V (continued)

Compound	ν NH glycosidic and phenolic νOH	ν C=O (amide I)	δ NH (amide II)	glycosidic δOH, ν C-O	phenolic ν C-O	ν COO^-	δ CF_3
32a	3700-3100	1655	1510	1250-1190 1110-930	o.b.		
32b	3700-3100	1650	1510	1250-1190 1100-940	o.b.		
32c	3700-3100	1655	1510	1250-1190 1100-940	o.b.		
68	3700-3100	1730 (ester) 1650 (amide I)	1510	1250-1190 1100-940	o.b.		
71	3700-3100	1725 (ester) 1650 (amide I)	1505	1270-1190 1100-940	o.b.		

Table V (continued)

Compound	ν NH glycosidic and phenolic νOH	ν C=O (amide I)	δ NH (amide II)	glycosidic δ OH, ν C-O	phenolic νC-O	νCOO^-	δCF_3
73	3700-3100	1725 (ester) 1645 (amide I)	1510		o.b.		
77	3700-3100	1650	1515		1230 1010		
78	3700-3100	1660	1515		1230 1010		1200 1135

Note:

The ν COO^- and δCF_3 data relate to the salifying acid.

o.b. = Overlapped bands.

TABLE VI: UV Data (λ max, nm)

	Compounds Nos. 1-23 and 25-31	compound No. 24
Methanol	280	282
0.1N HCl	278	280
Phosphate buffer pH 7.4	280	278
Phosphate buffer pH 9.0	280	283
0.1N KOH	298	298

TABLE VI: UV Data (λ max, nm)

	Compound 32a	Compound 32b and 32c	Compound 66
Methanol	272	276	
0.1N HCl	276	276	279
Phosphate buffer pH 7.4	276	276	279
Phosphate buffer pH 9.0	270	270	
0.1N KOH	294	294	296

TABLE VI: UV Data (λ max, nm)

	Compound 68	Compound 69	Compound 70
Methanol	280		
0.1N HCl	280	280	280
Phosphate buffer pH 7.4	280	280	280
Phosphate buffer pH 9.0	280	280	
0.1N KOH	298	296	298

TABLE VI: UV Data (λ max, nm)

	Compound 71	Compound 72	Compound 73
Methanol			
0.1N HCl	279	279	278
Phosphate buffer pH 7.4	280	280	279
Phosphate buffer pH 9.0			
0.1N KOH	298	298	298

TABLE VI: UV Data (λ max, nm)

	Compound 75	Compound 76 and 79	Compounds 77, 78 and 81
Methanol			
0.1N HCl	280	280	279
Phosphate buffer pH 7.4	280	280	280
Phosphate buffer pH 9.0			
0.1N KOH	298	298	298

TABLE VI: UV Data (λ max, nm)

	Compounds 80, 85-88, 93, 97, 100, and 101	Compounds 82 and 83	Compounds 84, and 92	Compound 103
Methanol		280		
0.1N HCl	279	278	280	280
Phosphate buffer pH 7.4	279	279	279	280
Phosphate buffer pH 9.0		280		
0.1N KOH	298	297	298	300

Table VII reports ^{1}H NMR data obtained at 250 MHz with a Bruker AM-250 Spectrometer in DMSO-d_6 at 20°C, at a sample concentration of 20 mg/ml (internal standard: TMS, = 0.00 ppm).

TABLE VII

^{1}H -NMR spectra (δ, ppm) in DMSO-d_6

Compound	
1	0.83, 1.13-1.17, 1.42, 2.02 (acyl chain); 1.87 (acetylglucosamine), 2.21 (N-CH_3); 3.48 (mannose); 5.58 (C_{27}H); 5.10 (C_{26}-H); 6.33-7.79 (aromatic protons)
2a	0.85, 1.23, 1.49, 2.08 (acyl chain); 1.93 (acetylglucosamine); 3.13 (alkylamino group); 4.36-5.71 (peptidic CH's); 6.41-7.92 (aromatic protons)
2b	0.83, 1.13-1.22, 2.00 (acyl chain); 0.96, 2.60 (ethyl groups); 1.88 (acetylglucosamine); 5.56 (C_{27}-H); 5.09 (C_{26}-H); 5.71-4.10 (peptidic CH's); 6.29-7.90 (aromatic protons)
3	0.84, 1.14, 1.42, 2.01 (acyl chain); 1.90 (acetylglucosamine); 1.70 (alkylamine); 5.57 (C_{27}-H); 5.09 (C_{26}-H)

TABLE VII (continued)

^{1}H -NMR spectra (δ, ppm) in DMSO-d_6

Compound	
4	0.84, 1.18, 1.43, 2.02 (acyl chain); 2.44, 3.62 (morpholine); 3.49 (mannose); 1.88 (acetylglucosamine); 5.58 (C_{27}-H); 5.10 (C_{26}-H)
5	0.87, 1.18, 1.44, 2.02 (acyl chain); 1.91 (acetylglucosamine); 3.49 (mannose); 5.57 (C_{27}-H); 5.10 (C_{26}-H)
6	0.84, 1.12, 1.38, 2.03 (acyl chain); 1.86 (acetylglucosamine); 3.46 (mannose); 5.56 (C_{27}-H); 5.10 (C_{26}-H); 6.34-7.89 (aromatic protons)
7	1.92 (acetylglucosamine); 2.76 (N-CH_3); 5.60 (C_{27}-H); 5.10 (C_{26}-H); 6.21-7.95 (aromatic protons)
8	
9	

TABLE VII (continued)

^1H -NMR spectra (δ, ppm) in DMSO-d_6

Compound	
10	1.92 (acetylglucosamine); 3.48 (mannose); 5.61 (C_{27}-H); 5.10 (C_{26}-H); 3.70 (morpholine); 6.23-7.85 (aromatic protons)
11	1.89 (acetylglucosamine); 3.03 (N-CH_2); 3.48 (mannose); 4.12-5.69 (peptide protons); 6.25-7.89 (aromatic protons)
12	1.89 (acetylglucosamine); 3.48 (mannose); 2.80 (N-CH_3); 5.60 (C_{27}-H); 5.10 (C_{26}-H); 6.34-7.93 (aromatic protons)
13	1.89 (acetylglucosamine); 2.74 (N-CH_3); 5.50 (C_{27}-H); 5.11 (C_{26}-H); 6.22-7.97 (aromatic protons)
14	1.80 (acetylglucosamine); 4.20-5.60 (peptide protons); 6.30-7.80 (aromatic protons)

TABLE VII (continued)

^{1}H -NMR spectra (δ, ppm) in DMSO-d_6

Compound	
15	1.90 (acetylglucosamine); 5.51 (C_{27}-H); 5.11 (C_{26}-H); 6.21-7.88 (aromatic protons)
16	1.82 (acetylglucosamine); 4.12-5.60 (peptidic protons); 7.92-6.34 (aromatic protons)
17	1.82 (acetylglucosamine); 3.70 ($COOCH_3$); 4.16-5.63 (peptidic protons); 7.92-6.33 (aromatic protons)
18	1.79 $\left[(CH_2)\text{-}CH_2\text{-}(CH_2)\right]_7$; 2.72 (N-$CH_3$); 2.96 (N-$CH_2$); 5.48 ($C_{27}$-H); 5.08 ($C_{26}$-H); 4.18-5.66 (peptidic CH'S); 6.21-7.78 (aromatic CH's)
19	2.64 (N-CH_2); 5.49 (C_{27}-H); 5.10 (C_{26}-H); 6.22-7.79 (aromatic protons)
20	0.87, 1.26, 1.39, 1.63, 3.16 (alkylamino groups); 1.90 (acetylglucosamine); 5.49 (C_{27}-H); 5.09 (C_{26}-H); 6.23-7.79 (aromatic CH's)

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(71) Applicant: **GRUPPO LEPETIT S.P.A.**
8, Via Roberto Lepetit
I-20124 Milano(IT)

(72) Inventor: **Malabarba, Adriano**
5-A, Via Roma
20082 Binasco Milano(IT)
Inventor: **Tarzia, Giorgio**
23, Via Valletta
21047 Saronno Varese(IT)

(74) Representative: **Sgarbi, Renato et al**
GRUPPO LEPETIT S.p.A. Patent and Trademark Department 34, Via Roberto Lepetit
I-21040 Gerenzano (Varese)(IT)

(54) Amides of teicoplanin compounds.

(57) The present invention relates to amide derivatives of teicoplanin compounds.
Teicoplanin is an antibiotic substance active mainly against gram-positive bacteria and its derivatives, which are collectively named "teicoplanin compounds", are the components, pseudoaglycones and aglycone thereof.
The compounds of the invention are obtained according to a proper amidation process and are active as antibiotics.

EP 0 218 099 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 86 11 2226

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A,D	EP-A-0 119 574 (LEPETIT) * Page 12, table 1; claims 1,2,9 *	1,21	C 07 K 9/00 C 07 K 7/06 A 61 K 37/02
A,D	EP-A-0 119 575 (LEPETIT) * Page 10, table 1; claims 1,2,11 *	1,21	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 K 9/00
C 07 K 7/00
A 61 K 37/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17-09-1987	BRENNAN J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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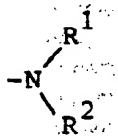
wherein

R represents hydrogen or a protecting group of the amine function

Y represents a group



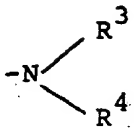
wherein

R^1 represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_6)alkyl, halogeno(C_2-C_6)alkyl, (C_1-C_6)alkoxy(C_2-C_6)alkyl amino(C_2-C_6)alkyl, (C_1-C_6)alkylamino(C_2-C_6)alkyl, di(C_1-C_6)alkylamino(C_2-C_6)alkyl

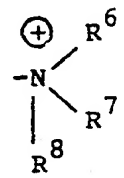
R^2 represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_6)alkyl, halogeno(C_2-C_6)alkyl, (C_1-C_6)alkoxy(C_2-C_6)alkyl, a nitrogen containing 5-6 membered heterocyclic ring

which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_6)alkyl substituents and one of the ring nitrogens may optionally bear a substituent R^5 selected from (C_1-C_6)alkyl, (C_4-C_7)cycloalkyl, phenyl optionally substituted with halogen or (C_1-C_6)alkyl, phenyl(C_1-C_6)alkyl, pyridyl, (C_1-C_6)alkylpyridinio, and when the ring is wholly saturated two of the ring members may optionally be bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or - N [-(C_1-C_6)alkyl];

a group -alk-W wherein "alk" represents a linear alkylene chain of 1 to 8 carbon atoms which is optionally substituted with a substituent selected from (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, hydroxy, carboxy, aminocarbonyl, (C_1-C_6)alkylaminocarbonyl, di(C_1-C_6)alkylaminocarbonyl, (C_1-C_6)alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, and W represents a carboxy, (C_1-C_6)alkoxycarbonyl, phenyl(C_1-C_6)alkoxycarbonyl, aminocarbonyl, (C_1-C_6)aminocarbonyl, di(C_1-C_6)aminocarbonyl, pentosaminocarbonyl, hexosaminocarbonyl, ureido, guanidino, a nitrogen containing 5-6 membered heterocyclic ring defined as above, a group of the formula



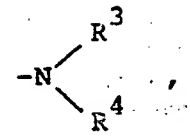
wherein R^3 and R^4 each independently represent hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_6)alkyl and halogeno(C_2-C_6)alkyl, or R^4 represents phenylmethyloxycarbonyl and R^3 represents hydrogen; a group of the formula

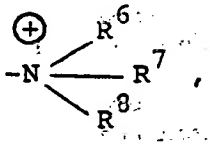


wherein R^6, R^7 and R^8 each independently represent a (C_1-C_4)alkyl,

or R^1 and R^2 taken together with the adjacent nitrogen atom represent a saturated 5-7 membered heterocyclic ring which may optionally bear one to two (C_1-C_4)alkyl substituents on the ring carbons and may contain a further heterogroup selected from -O-, -S-, and -NR^5-wherein R^5 is defined as above;

a group





ureido, guanidino or a nitrogen containing 5-6 membered heterocyclic ring as defined above directly connected with the "alk" moiety through a bond with a ring nitrogen atom, the linear alkylene "alk" moiety must be of at least two carbon atoms;

and the addition salts thereof, which comprises:

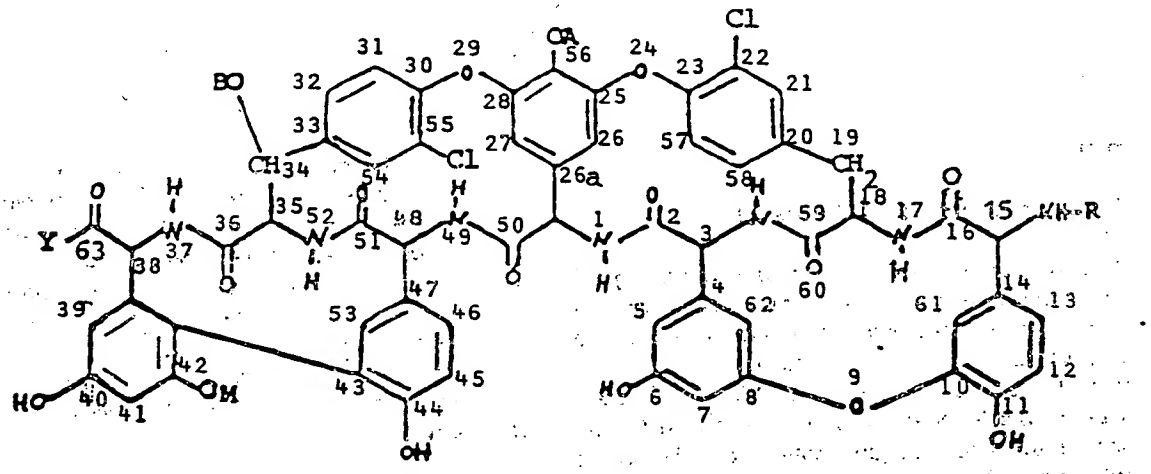
A represents hydrogen or -N[(C_{10}-C_{11})-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl,

B represents hydrogen or N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl;

with the proviso that B represents hydrogen only when A and M are simultaneously hydrogen and M represents hydrogen only when A is hydrogen and with the further proviso that when W represents a group

a) reacting a teicoplanin starting material selected from teicoplanin as obtained according to US Patent 4239751, any further purification thereof, teicoplanin A_2 complex, a compoupnd of formula I



wherein R is hydrogen or a protecting group of the amine function, Y is hydroxy, A represents hydrogen or -N[(C_{10}-C_{11})aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl, B represents hydrogen or N-acetyl-β-D-2-deoxy-2-aminoglucopyranosyl, M represents hydrogen or α-D-mannopyranosyl, with the proviso that B may represent hydrogen only when A and M are simultaneously hydrogen and M may represent hydrogen only when A is hydrogen, a salt thereof or a mixture thereof in any proportion with a molar excess of an amine of formula HNR^1R^2, wherein R^1 and R^2 are defined as above and wherein the reactive functions, other than the amino function to be reacted with the carboxyl moiety of the teicoplanin starting material, are protected by means of known per se protecting groups, in an inert organic solvent, and in the presence of a slight molar excess of a condensing agent,

b) optionally transforming an amide compound of formula I wherein A, B and M represent a sugar moiety as above defined into the corresponding compound wherein B and M are as above and A is hydrogen by means of controlled acid hydrolysis in strong concentrated aqueous organic acid;

c) optionally transforming an amide compound of formula I wherein A, B and M represent a sugar moiety as above defined or A represents hydrogen and B and M represent sugar moieties as above defined into the corresponding amide compounds or formula I wherein A and M represent hydrogen and B represents a sugar moiety as defined by means of a selective hydrolysis with a strong acid in the presence of a polar aprotic solvent selected from ethers, ketones, and mixtures thereof which are liquid at room temperature; or

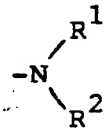
d) optionally transforming an amide compound of formula I wherein A, and M represent sugar moieties as defined above, an amid compound of formula I wherein A represents hydrogen and B and M represent the above defined sugar moieties, or an amide compound of formula I wherein A and M represent hydrogen, and B represents a sugar moiety as above defined, into the corresponding amide compound of formula I wherein A, B and M represent hydrogen atoms by means of a selective hydrolysis in an organic protic solvent selected from aliphatic acids and alpha-halogenated aliphatic acids which at the reaction temperature are liquids, aliphatic and cycloaliphatic alkanols which at the reaction temperature are liquids slightly mixable with water, phenylsubstituted lower alkanols wherein the phenyl moiety may optionally carry (C_1-C_4)alkyl, (C_1-C_4) alkoxy or halo rests which at the reaction temperature are liquids slightly mixable with water, and beta-polyhalogenated lower alkanols, which at the reaction temperature are liquids; in the presence of a strong acid, compatible with the solvent, selected from strong mineral acids, strong organic acids and strong acid cation exchanger resins in the hydrogen form and at a temperature between 20°C and 100°C.

2) A process as claimed in claim 1 for preparing a compound formula I wherein R is hydrogen.

3) A process as claimed in claim 1 for preparing a compound formula I wherein R and R' are hydrogen atoms.

4) A process as claimed in claim 1 for preparing a compound of formula I wherein R represents hydrogen

Y represents a group



wherein

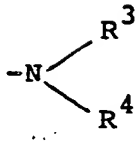
R^1 represents hydrogen, (C_1-C_4)alkyl,

R^2 represents (C_1-C_4)alkyl, a nitrogen containing 5-6 membered heterocyclic ring which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents and one of the ring nitrogens may optionally bear a substituent R^5 selected from (C_1-C_4)alkyl, (C_4-C_7)-cycloalkyl, phenyl, and pyridyl;

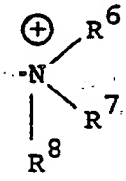
a wholly saturated nitrogen containing 5-6 membered heterocylic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N(alkyl)- [(C_1-C_4)-alkyl];

a group -alk-W wherein "alk" represents a linear alkylene chain of 1 to 8 carbon atoms which is

optionally substituted with a substituent selected from (C_1-C_4)alkyl, carboxy, aminocarbonyl, (C_1-C_4)-alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, and W represents a carboxy, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, aminocarbonyl, (C_1-C_4)aminocarbonyl, di(C_1-C_4)aminocarbonyl, glucosaminocarbonyl, ureido, guanidino, a nitrogen containing 5-6 membered heterocylic ring which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents and one of the ring nitrogens may optionally bear a substituent R^5 s lected from (C_1-C_4)alkyl, (C_4-C_7)cycloalkyl, phenyl, and pyridyl; a wholly saturated nitrogen containing 5-6 membered heterocylic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring m mbers are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or - N [(C_1-C_4)-alkyl]; a group of the formula



wherein R^3 and R^4 each independently represent hydrogen (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl and halogeno(C_2-C_3)alkyl, or R^4 represents phenylmethyloxycarbonyl and R^3 represents hydrogen; a group of the formula



wherein R^6, R^7 and R^8 each independently represent a (C_1-C_4)alkyl,

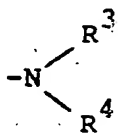
or R^7 and R^8 taken together with the adjacent nitrogen atom represent a saturated 5-7 membered heterocylic ring which may optionally bear one to two (C_1-C_4)alkyl substituents on the ring carbons and may contain a further heterogroup selected from -O-, -S-, and -NR^5-wherein R^5 is defined as above;

A represents hydrogen or -N[(C_{10}-C_{11})-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl,

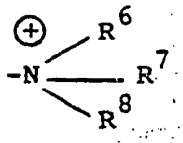
B represents hydrogen or N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl;

with the proviso that B represents hydrogen only when A and M are simultaneously hydrog n and M represents hydrogen only when A is hydrogen and with further proviso that when W represents a group



a group



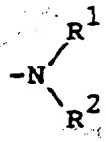
ureido, guanidino or a nitrogen containing 5-6 membered heterocylic ring as defined above directly connected with the "alk" moiety through a bond with a ring nitrogen atom, the linear alkylene "alk" moiety must be of at least two carbon atoms;

and the addition salts thereof.

5) A process as claimed in claim 1 for preparing a compound of formula I wherein

R represents hydrogen or a protecting group of the amine function

Y represents a group



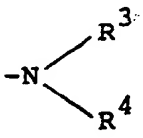
wherein

R^1 represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl, halogeno(C_2-C_4)alkyl, (C_1-C_4)alkoxy(C_2-C_4)-alkyl, amino (C_2-C_4)alkyl, (C_1-C_4)alkylamino(C_2-C_4)-alkyl, di(C_1-C_4)alkylamino(C_2-C_4)alkyl

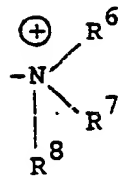
R^2 represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl, halogeno(C_2-C_4)alkyl, (C_1-C_4)alkoxy(C_2-C_4)-alkyl,

a nitrogen containing 5-6 membered heterocylic ring which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein one of the ring nitrogens may optionally bear a substituent R^5 selected from (C_1-C_4)alkyl, (C_4-C_7)-cycloalkyl, phenyl optionally substituted with halogen or (C_1-C_4)alkyl, phenyl(C_1-C_4)alkyl, pyridyl, (C_1-C_4)alkylpyridinio;

a group -alk-W wherein "alk" represents a linear alkylene chain of 1 to 6 carbon atoms which is optionally substituted with a substituent selected from (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, hydroxy, carboxy, aminocarbonyl, (C_1-C_4)alkylaminocarbonyl, di-(C_1-C_4)alkylaminocarbonyl, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, and W represents a carboxy, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)-alkoxycarbonyl, aminocarbonyl, (C_1-C_4)-aminocarbonyl, di(C_1-C_4)aminocarbonyl, pentosaminocarbonyl, hexosaminocarbonyl, ureido, guanidino, a nitrogen containing 5-6 membered heterocyclic ring defined as above, a group of the formula



wherein R^3 and R^4 each independently represent hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl and halogeno(C_2-C_4)alkyl, or R^4 represents phenylmethyloxycarbonyl and R^3 represents hydrogen; a group of the formula



wherein R^6, R^7 and R^8 each independently represent a (C_1-C_4)alkyl,

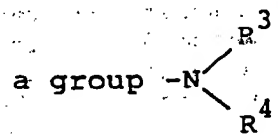
or R^1 and R^2 taken together with the adjacent nitrogen atom represent a saturated 5-7 membered heterocylic ring which may optionally bear one to two (C_1-C_4)alkyl substituents on the ring carbons and may contain a further heterogroup selected from -O-, -S-, and -NR^5-wherein R^5 is defined as above;

A represents hydrogen or -N[(C_{10}-C_{11})-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl,

B represents hydrogen or N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl;

with the proviso that B represents hydrogen only when A and M are simultaneously hydrogen and M represents hydrogen only when A is hydrogen and with the further proviso that when W represents a group



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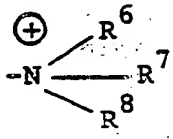


ureido, guanidino or a nitrogen containing 5-6 membered heterocylic ring as defined above directly connected with the "alk" moiety through a bond with a ring nitrogen atom, the linear alkylene "alk" moiety must be of at least two carbon atoms;

and the addition salts thereof.

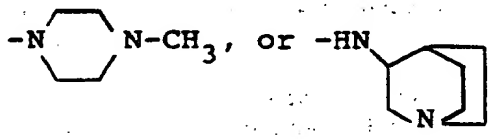
6) A process according to claim 1 for preparing a compound of formula I wherein R represents hydrogen; R^1 represents hydrogen or (C_1-C_4)alkyl, R^2 represents a wholly saturated nitrogen containing 5-6 membered heterocylic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N [(C_1-C_4)alkyl];

or a group -alk-W wherein alk represents a linear alkylene chain or 1 to 3 carbon atoms and W is wholly saturated nitrogen containing 5-6 membered heterocylic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N [(C_1-C_4)-alkyl]; and the pharmaceutically acceptable addition salts thereof.

7) A process according to claim 1 for preparing a compound of formula I wherein A, B, and M either represent the sugar moieties as above defined or each represents a hydrogen atom.

8) A process according to claim 1 for preparing a compound of formula I wherein A, B and M either simultaneously represent the sugar moieties defined above or simultaneously represent hydrogen atoms, R represents hydrogen, and NR^1R^2 represents a group -HN(alk)W wherein "alk" represents

a linear alkylene chain of 2, 3, 4, 5, 6, 7 or 8 units and W represents a group selected from: $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, and $-N(CH_3)(C_2H_5)$, or a group $-HNCH(COOCH_3)(CH_2)_4NH_2$,



9) A process according to claim 1 for preparing a compound of formula I wherein A represents β-D-2-deoxy-2-(8-methylnonanoyl)-amino-glucopyranosyl, B represents β-D-2-deoxy-2-acetylamino-glucopyranosyl and M represents α-D-mannopyransosyl.

10) A process as claimed in claim 1 wherein the starting material is a compound wherein R represents a protecting group of the amine function and at least one among A and M in the final compound is hydrogen.

11) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein the protecting group R of the teicoplanin starting material is a N-protecting group resulting from a carbamate forming reagent characterized by one of the following oxycarbonyl groups: 1,1-dimethylpropynyloxycarbonyl, t-butyloxycarbonyl, vinyloxycarbonyl, aryloxycarbonyl, cinnamyloxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl-3,4-dimethoxy-6-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 5-benzisoxazolymethyloxycarbonyl, 9-anthranylmethyloxycarbonyl, diphenylmethyloxycarbonyl, isonicotinyloxycarbonyl, diphenylmethyloxycarbonyl, isonicotinyloxycarbonyl, S-benzyloxycarbonyl.

12) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8, or 9 wherein the protecting group R of the teicoplanin starting material is a N-protecting group resulting from a Schiff base forming reagent represented by benzaldehyde or a benzaldehyde derivative substituted on the phenyl ring with a hydroxy substituent.

13) A process as in any of the claims 1, 10, 11 and 12 wherein the amine HNR^1R^2 contains further reactive functions which may unfavorably interfere with the amidation reaction course and said functions are protected by methods per se kniwn in the art.

14) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein the inert organic solvent is a organic aprotic solvent.

15) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein the inert organic solvent is selected from dimethylformamide, dimethoxyethane, hexamethylphosphoramide, dimethylsulfoxide, benzene, toluene and mixtures thereof.

16) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein the condensing agent is selected from (C_1-C_4)alkyl, phenyl or heterocyclic phosphorazidates such as diphenyl phosphorazidate (DPPA), diethyl phosphorazidate, di(4-nitrophenyl)phosphorazidate, dimorpholylphosphorazidate and diphenylphosphorochloridrate.

17) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein the condensing agent is diphenylphosphorazidate (DPPA).

18) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein the condensing agent is present in a molar proportion of from 1.2 to 1.7 the teicoplanin starting material.

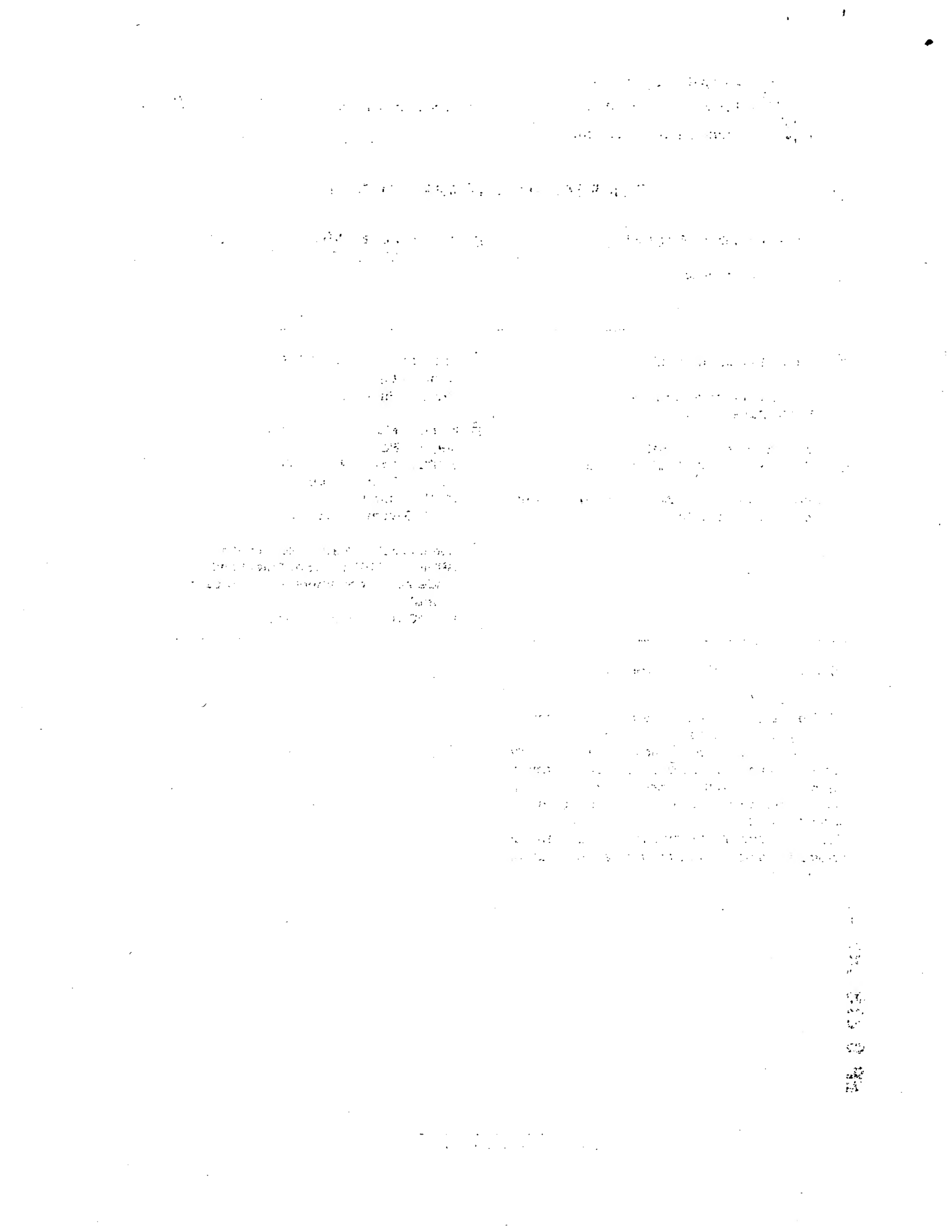
19) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein the amine HNR^1R^2 is added as a corresponding acid addition salt and the reaction is conducted in the presence of a 2 to 4-fold molar excess of a base capable or freeing the amine HNR^1R^2 from its salt.

20) A process as claimed in claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 wherein the reaction is conducted at a temperature between 0°C and 20°C.

21) A process as claimed in claim 1, optional step b), wherein the concentrated organic acid is 75 to 95% aqueous trifluoroacetic acid and th reaction temperature is between 10°C and 50°C.

22) A process as claimed in claim 1, optional step c), wherein the strong acid is a concentrated mineral acid.

23) A process as claimed in claim 1, optional step d), wherein the strong acid is a mineral acid, the solvent is an haloalkanol and the hydrolysis is conducted at a temperature between 65°C and 85°C.



12) A process as claimed in claim 10 wherein the protecting group R of the teicoplanin starting material is a N-protecting group resulting from a carbamate forming reagent characterized by one of the following oxycarbonyl groups: 1,1-dimethylpropynyloxycarbonyl, t-butyloxycarbonyl, vinyloxycarbonyl, aryloxycarbonyl, cinnamyloxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl-3,4-dimethoxy-6-nitrobenzyloxycarbonyl, 2,4-dichlorobenzyloxycarbonyl, 5-benzisoxazolylmethyloxycarbonyl, 9-anthranylmethyloxycarbonyl, diphenylmethyloxycarbonyl, isonicotinyloxycarbonyl, diphenylmethyloxycarbonyl, isonicotinyloxycarbonyl, S-benzyloxycarbonyl.

13) A process as claimed in claim 10 wherein the protecting group R of the teicoplanin starting material is a N-protecting group resulting from a Schiff base forming reagent represented by benzaldehyde or a benzaldehyde derivative substituted on the phenyl ring with an hydroxy substituent.

14) A process as in any of the claims 10, 11, 12 and 13 wherein the amine HNR^1R^2 contains further reactive functins which may unfavorably interfere with the amidation reaction course and said functions are protected by methods per se known in the art.

15) A process as claimed in claim 10 wherein the inert organic solvent is selected from dimethylformamide, dimethoxyethane, hexamethylphosphoramide, dimethylsulfoxide, benzene, toluene and mixtures thereof.

16) A process as claimed in claim 10 wherein the condensing agent is selected from (C_1-C_4)alkyl, phenyl or heterocyclic phosphorazidates such as diphenyl phosphorazidate (DPPA), diethyl phosphorazidate, di(4-nitrophenyl)phosphorazidate, dimorpholylphosphorazidate and diphenylphosphorochloridrate.

17) A process as claimed in claim 10 wherein th condensing agent is present in a molar proportion of from 1.2 to 1.7 the teicoplanin starting material.

18) A process as claimed in claim 10 wherein the amine HNR^1R^2 is added as a corresponding acid addition salt and the reaction is conducted in the presence of a 2 to 4-fold molar excess of a base capable of freeing the amine HNR^1R^2 from its salt.

19) A process as claimed in claim 10 wherein the reaction is conducted at a temperature between 0°C and 20°C.

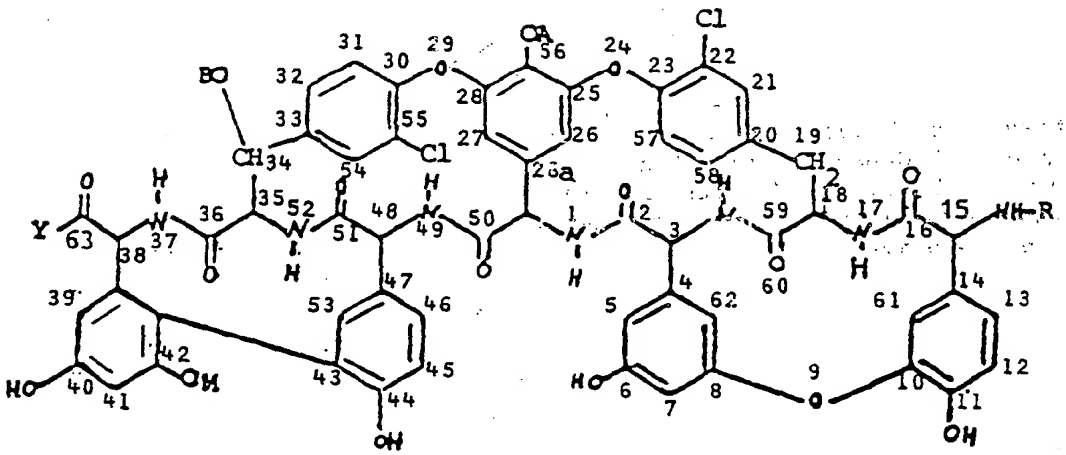
20) A compound as in claim 1 for use as a medicine.

21) Use of a substance of claim 1 for the manufacture of a medicament for use as antibacterial.

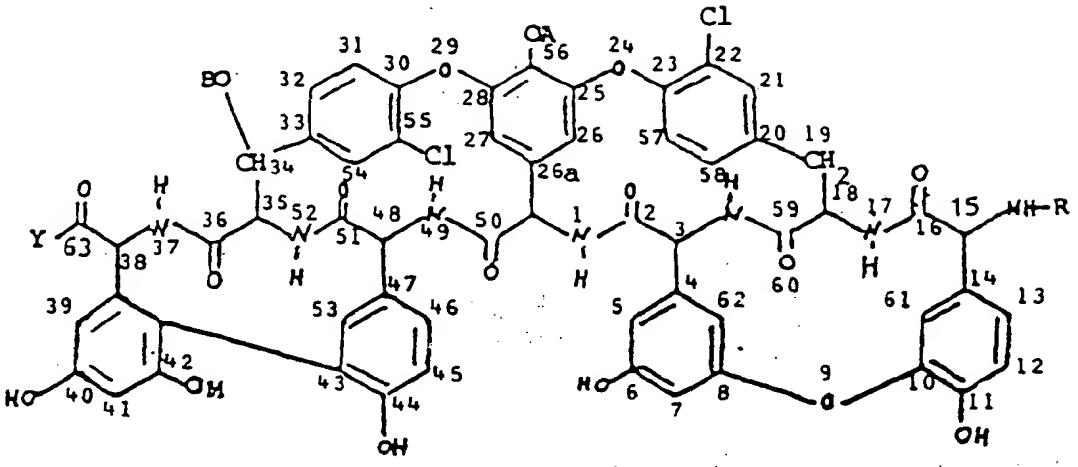
22) A pharmaceutical composition comprising a compound of claim 1 in admixture with a pharmaceutically acceptable carrier.

Claims for the following Contracting State : AT

1) A process for preparing an amide of a teicoplanin compound having the formula



a) reacting a teicoplanin starting material selected from teicoplanin as obtained according to US patent 4239751, any further purification thereof, teicoplanin A_2 complex, a compound of formula I



wherein R is hydrogen or a protecting group of the amine function, Y is hydroxy, A represents hydrogen or -N[(C_{10}-C_{11})aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl, B represents hydrogen or N-acetyl-β-D-2-deoxy-2-aminoglucopyranosyl, M represents hydrogen or α-D-mannopyranosyl, with the proviso that B may represent hydrogen only when A and M are simultaneously hydrogen and M may represent hydrogen only when A is hydrogen, a salt thereof or a mixture thereof in any proportion with a molar excess of an amine of formula HNR^1R^2, wherein R^1 and R^2 are defined as above and wherein the reactive functions, other than the amino function to be reacted with the carboxyl moiety of the teicoplanin starting material, are protected by means of known per se protecting groups, in an inert organic solvent, and in the presence of a slight molar excess of a condensing agent;

b) optionally transforming an amide compound of formula I wherein A, B and M represent a sugar moiety as above defined into the corresponding compound wherein B and M are as above and A is hydrogen by means of controlled acid hydrolysis in strong concentrated aqueous organic acid;

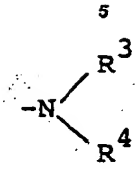
c) optionally transforming an amide compound of formula I wherein A, B and M represent a sugar moiety as above defined or A represents hydrogen and B and M represent sugar moieties as above defined into the corresponding amide compounds of formula I wherein A and M represent hydrogen and B represents a sugar moiety as defined by means of a selective hydrolysis with a strong acid in the presence of a polar aprotic solvent selected from ethers, ketones, and mixtures thereof which are liquid at room temperature; or

d) optionally transforming an amide compound of formula I wherein A, B and M represent sugar moieties as defined above, an amide compound of formula I wherein A represents hydrogen and B and M represent the above defined sugar moieties, or an amide compound of formula I wherein A and M represent hydrogen, and B represents a sugar moiety as above defined, into the corresponding amide compound of formula I wherein A, B and M represent hydrogen atoms by means of a selective hydrolysis in an organic protic solvent selected from aliphatic acids and alpha-halogenated aliphatic acids which at the reaction temperature are liquids, aliphatic and cycloaliphatic alkanols which at the reaction temperature are liquids slightly mixable with water, phenylsubstituted lower alkanols wherein the phenyl moiety may optionally carry (C_1-C_4)alkyl, (C_1-C_4)alkoxy or halo rests which at the reaction temperature are liquids slightly mixable with water, and beta-polyhalogenated lower alkanols, which at the reaction temperature are liquids; in the presence of a strong acid, compatible with the solvent, selected from strong mineral acids, strong organic acids and strong acid cation exchanger resins in the hydrogen form and at a temperature between 20°C and 100°C.

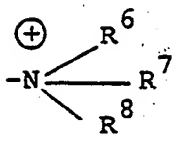
11) A process as claimed in claim 10 wherein the starting material is a compound wherein R represents a protecting group of the amine function and at least one among A and M in the final compound is hydrogen.

drogen and with the further proviso that when W represents

a group



a group



ureido, guanidino or a nitrogen containing 5-6 membered heterocyclic ring as defined above directly connected with the "alk" moiety through a bond with a ring nitrogen atom, the linear alkylene "alk" moiety must be of at least two carbon atoms;

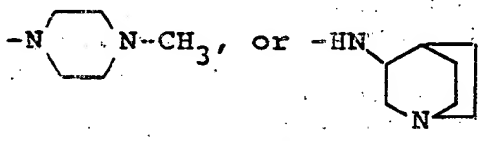
and the addition salts thereof.

6) A compound as claimed in claim 1 wherein R represents hydrogen; R^1 represents hydrogen or (C_1-C_4)alkyl, R^2 represents a wholly saturated nitrogen containing 5-6 membered heterocyclic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or - $\overset{+}{N}$ [(C_1-C_4)alkyl];

or a group -alk-W wherein alk represents a linear alkylene chain of 1 to 3 carbon atoms and W is a wholly saturated nitrogen containing 5-6 membered heterocyclic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or - $\overset{+}{N}$ [(C_1-C_4)-alkyl]; and the pharmaceutically acceptable addition salts thereof.

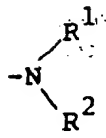
7) A compound as claimed in claim 1 wherein A, B, and M either represent the sugar moieties as above defined or each represents a hydrogen atom.

8) A compound as claimed in claim 1 wherein A, B, and M either simultaneously represent the sugar moieties defined above or simultaneously represent hydrogen atoms, R represents hydrogen, and NR^1R^2 represents a group -HN(alk)W wherein "alk" represents a linear alkylene chain of 2, 3, 4, 5, 6, 7, or 8 units and W represents a group selected from $-NH_2$, $-NHCH_3$, $-NHC_2H_5$, $-N(CH_3)_2$, $-N(C_2H_5)_2$, and $-N(CH_3)(C_2H_5)$, or a group $-HNCH(COOCH_3)(CH_2)_4NH_2$,



9) A compound of claim 1 wherein A represents β-D-2-deoxy-2-(8-methylnonanoyl)-amino-glucopyranosyl, B represents β-D-2-deoxy-2-acetylamino-glucopyranosyl and M represents α-D-mannopyranosyl.

10) A process for preparing a compound of claims 1, 2, 3, 4, 5, 6, 7, 8 or 9 which comprises:



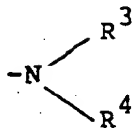
wherein

R^1 represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl, halogeno(C_2-C_4)alkyl, (C_1-C_4)alkoxy(C_2-C_4)-alkyl, amino(C_2-C_4)alkyl, (C_1-C_4)alkylamino(C_2-C_4)-alkyl, di(C_1-C_4)alkylamino(C_2-C_4)alkyl

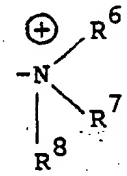
R^2 represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl, halogeno(C_2-C_4)alkyl, (C_1-C_4)alkoxy(C_2-C_4)-alkyl, a nitrogen containing 5-6 membered heterocyclic ring

which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein one of the ring nitrogens may optionally bear a substituent R^5 selected from (C_1-C_4)alkyl, (C_4-C_7)-cycloalkyl, phenyl optionally substituted with halogen or (C_1-C_4)alkyl, phenyl(C_1-C_4)alkyl, pyridyl, (C_1-C_4)alkylpyridinio;

a group -alk-W wherein "alk" represents a linear alkylene chain of 1 to 6 carbon atoms which is optionally substituted with a substituent selected from (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, hydroxy, carboxy, aminocarbonyl, (C_1-C_4)alkylaminocarbonyl, di-(C_1-C_4)alkylaminocarbonyl, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl; and W represents a carboxy,(C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)-alkoxycarbonyl, aminocarbonyl, (C_1-C_4)-aminocarbonyl, di(C_1-C_4)aminocarbonyl, pentosaminocarbonyl, hexosaminocarbonyl, ureido, guanidino, a nitrogen containing 5-6 membered heterocyclic ring defined as above, a group of the formula



wherein R^3 and R^4 each independently represent hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl and halogeno(C_2-C_4)alkyl, or R^4 represents phenylmethyloxycarbonyl and R^3 represents hydrogen; a group of the formula



wherein R^6, R^7 and R^8 each independently represent a (C_1-C_4)alkyl,

or R^1 and R^2 taken together with the adjacent nitrogen atom represent a saturated 5-7 membered heterocyclic ring which may optionally bear one to two (C_1-C_4)alkyl substituents on the ring carbons and may contain a further heterogroup selected from -O-, -S-, and -NR^5-wherein R^5 is defined as above;

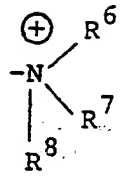
A represents hydrogen or -N[(C_{10}-C_{11})-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl,

B represents hydrogen or N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl;

with the proviso that B represents hydrogen only when A and M are simultaneously hydrogen and M represents hydrogen only when A is hy-

wherein R^3 and R^4 each independently represent hydrogen, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_2\text{-}C_4)$alkyl and halogeno$(C_2\text{-}C_4)$ alkyl,or R^4 represents phenylmethyloxycarbonyl and R^3 represents hydrogen; a group of the formula

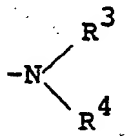


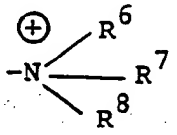
wherein R^6, R^7 and R^8 each independently represent a $(C_1\text{-}C_4)$alkyl,

or R^1 and R^2 taken together with the adjacent nitrogen atom represent a saturated 5-7 membered heterocyclic ring which may optionally bear one to two $(C_1\text{-}C_4)$alkyl substituents on the ring carbons and may contain a further heterogroup selected from -O-, -S-, and $-NR^5$-wherein R^5 is defined as above;

A represents hydrogen or -N[$(C_{10}\text{-}C_{11})$-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl,

, a group





, ureido, guanidino or a nitrogen containing 5-6 membered heterocyclic ring as defined above directly connected with the "alk" moiety through a bond with a ring nitrogen atom, the linear alkylene "alk" moiety must be of at least two carbon atoms;

and the addition salts thereof.

B represents hydrogen or N-acetyl-β-D-2-deoxy-2-amino--glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl;

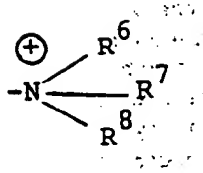
with the proviso that B represents hydrogen only when A and M are simultaneously hydrogen and M represents hydrogen only when A is hydrogen and with the further proviso that when W represents

a group

5) A compound as claimed in claims 1, 2 or 3 wherein

R represents hydrogen or a protecting group of the amine function

Y represents a group



, ureido, guanidino or a nitrogen containing 5-6 membered heterocyclic ring as defined above directly connected with the "alk" moiety through a bond with a ring nitrogen atom, the linear alkylene "alk" moiety must be of at least two carbon atoms;

and the addition salts thereof.

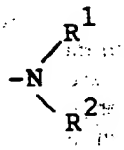
2) a compound as claimed in claim 1 wherein R is hydrogen.

3) A compound as claimed in claims 1 or 2 wherein R and R' are hydrogen atoms.

4) A compound as claimed in claims 1, 2 or 3 wherein

R represents hydrogen

Y represents a group



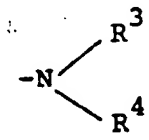
wherein

R' represents hydrogen, (C_1-C_6)alkyl,

R^2 represents (C_1-C_6)alkyl, a nitrogen containing 5-6 membered heterocyclic ring which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents and one of the ring nitrogens may optionally bear a substituent R^5 selected from (C_1-C_4)alkyl, (C_4-C_7)-cycloalkyl, phenyl, and pyridyl;

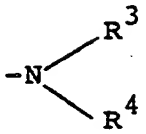
a wholly saturated nitrogen containing 5-6 membered heterocyclic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N(R')- [(C_1-C_4)-alkyl];

a group -alk-W wherein "alk" represents a linear alkylene chain of 1 to 8 carbon toms which is optionally substituted with a substituent selected from (C_1-C_4)alkyl, carboxy, aminocarbonyl, (C_1-C_4)-alkylaminocarbonyl, di(C_1-C_4)alkylaminocarbonyl, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, aminocarbonyl, (C_1-C_4)aminocarbonyl, di(C_1-C_4)aminocarbonyl, glucosaminocarbonyl, ureido, guanidino, a nitrogen containing 5-6 membered heterocyclic ring which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents and one of the ring nitrogens may optionally bear a substituent R^5 selected from (C_1-C_4)alkyl, (C_4-C_7) cycloalkyl, phenyl, and pyridyl; a wholly saturated nitrogen containing 5-6 membered heterocyclic ring which may contain a further N atom wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, one of the ring nitrogens may optionally bear a substituent R^5 representing (C_1-C_4)alkyl and two of the ring members are bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or -N(R')- [(C_1-C_4)-alkyl]; a group of the formula

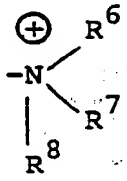


(C_1-C_4)alkyl, (C_4-C_7)cycloalkyl, phenyl optionally substituted with halogen or (C_1-C_4)alkyl, phenyl(C_1-C_4)alkyl, pyridyl, (C_1-C_4)alkylpyridinio, and when the ring is wholly saturated two of the ring members may optionally be bridged by an alkylene chain of 1 to 3 carbon atoms wherein one of the methylene groups may optionally be replaced by -NH-or-N [-(C_1-C_4)alkyl];

a group -alk-W wherein "alk" represents a linear alkylene chain of 1 to 8 carbon atoms which is optionally substituted with a substituent selected from (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, hydroxy, carboxy, aminocarbonyl, (C_1-C_4)alkylaminocarbonyl, di-(C_1-C_4)alkylaminocarbonyl, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)alkoxycarbonyl, and W represents a carboxy, (C_1-C_4)alkoxycarbonyl, phenyl(C_1-C_4)-alkoxycarbonyl, aminocarbonyl, (C_1-C_4)-aminocarbonyl, di(C_1-C_4)aminocarbonyl, pentosaminocarbonyl, hexosaminocarbonyl, ureido, guanidino, a nitrogen containing 5-6 membered heterocyclic ring defined as above, a group of the formula



wherein R^3 and R^4 each independently represent hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_4)alkyl and halogeno(C_2-C_4) alkyl, or R^4 represents phenylmethyloxycarbonyl and R^3 represents hydrogen; a group of the formula



wherein R^6, R^7 and R^8 each independently represent a (C_1-C_4)alkyl,

or R^1 and R^2 taken together with the adjacent nitrogen atom represent a saturated 5-7 membered heterocyclic ring which may not optionally bear one to two (C_1-C_4)alkyl substituents on the ring carbons and may contain a further heterogroup selected from -O-, -S-, and -NR^5-wherein R^5 is defined as above;

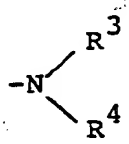
A represents hydrogen or -N[(C_1-C_{11})-aliphatic acyl]-β-D-2-deoxy-2-amino-glucopyranosyl,

B represents hydrogen or N-acetyl-β-D-2-deoxy-2-amino-glucopyranosyl,

M represents hydrogen or α-D-mannopyranosyl;

with the proviso that B represents hydrogen only when A and M are simultaneously hydrogen and M represents hydrogen only when A is hydrogen and with the further proviso that when W represents

a group



, a group

displacement of the nitro-group according to procedure A_6).

Preparation of compounds 32a, 59, 60 and 98

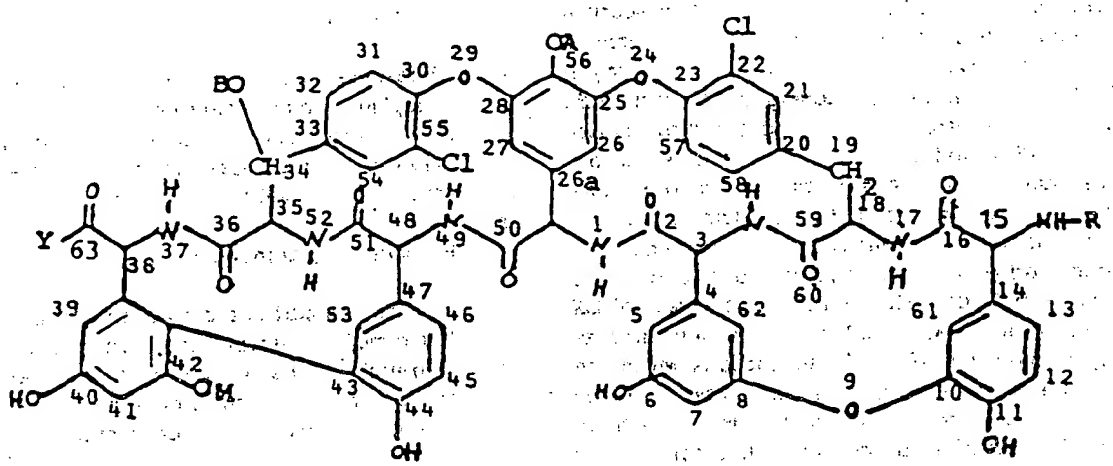
The first step, starting rom teicoplanin A_2 (complex or a single component thereof), N^{15}-t-BOC deglucoteicoplanin or N^{15}-CBzO deglucoteicoplanin and the proper N_{ω}-nitro-arginine derivative, yields the respective protected compounds of the title. By treatment with 100% trifluoroacetic acid the N^{15}-t-BOPC protecting group is removed and by catalytic hydrogenation over 5-10% Pd/C also the N^{15}-CBzO and benzyl groups are displaced.

The N_{ω}-nitro derivatives of compounds 32a, 59, 60 and 98 are thus obtained. The N_{ω}-nitro group is subsequently removed following procedure A_6, as described in Example 19, yielding the compounds of the title.

Claims

Claims for the following Contracting States : BE CH DE FR GB IT LU NL SE

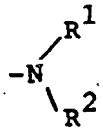
1) An amide of a teicoplanin compound having the formula



wherein

R represents hydrogen or a protecting group of the amine function

Y represents a group



wherein

R¹ represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_6)alkyl, halogeno(C_2-C_6)alkyl, (C_1-C_6)alkoxy(C_2-C_6)-alkyl, amino(C_2-C_6)alkyl, (C_1-C_6)alkylamino(C_2-C_6)-alkyl, di(C_1-C_4)alkylamino(C_2-C_6)alkyl

R² represents hydrogen, (C_1-C_6)alkyl, hydroxy(C_2-C_6)alkyl, halogeno(C_2-C_6)alkyl, (C_1-C_6)alkoxy(C_2-C_6)-alkyl, a nitrogen containing 5-6 membered heterocyclic ring

which may be unsaturated, partially saturated or wholly saturated and may contain 1 to 3 further heteroatoms selected from, N, S and O wherein 1 to 3 of the ring carbons may optionally bear (C_1-C_4)alkyl substituents, and one of the ring nitrogens may optionally bear a substituent R⁵ selected from

solutions are combined, washed with 600 ml of H_2O (2 x 300 ml) and concentrated to a small volume - (50 ml) under vacuum at 40°C. By adding ethyl ether (350 ml) a solid separates which is collected and dried in vacuo at room temperature overnight, yielding the title compound.

EXAMPLE 17

(Procedure F_3: esterification of a compound of formula I wherein the group $-NR^1R^2$ contains carboxylic functions)

Preparation of compound 51

A stirred suspension of 4.1 g (~2 mmol) of compound 27 in 200 ml of 2.5 M HCl is absolute ethanol is refluxed for 5 h. The reaction mixture is then concentrated to a small volume (~40 ml) at 50°C under vacuum. By adding ethyl either (~260 ml) a solid separates which is collected by filtration and re-dissolved in 50 ml of a mixture acetonitrile:water, 1:1 (v/v). After adding 150 ml of H_2O, the resulting solution is loaded on a column of 400 g of silanized silica-gel (Merck) in H_2O. The column is developed with a linear gradient from 20 to 70% of CH_3CN in 0.001N HCl in 20 h at the rate of 200 ml/h, while collecting 20 ml of fractions and assaying them by HPLC. Those fractions which contain the pure title compound are combined and the resulting solution is brought to pH 8.0 with 2% $NaHCO_3$. After extraction with n-butanol (v/v), 1N HCl (2.5 ml 1N HCl per 100 ml of the butanolic solution) is added and the resulting organic solution is concentrated to a small volume thus obtaining a dry butanolic suspension that by adding ethyl ether (v/v) gives a solid which is collected by filtration and dried in vacuo at 40°C overnight, yielding 0.97 g of pure compound 51, as the di-hydrochloride.

EXAMPLE 18

(Procedure G: separation of the amides of teicoplanin A_2 complex into their components by reverse-phase column chromatography)

Preparation of compounds 2b, 32b, 32c, and 71

A solution of 5 mmol of the starting amide derivative of teicoplanin A_2 complex in 250 ml of a mixture acetonitrile:water, 1:1 (v/v) is adjusted to pH 3.5 with 1N HCl, afterwards most of the organic solvent is evaporated under vacuum at 20°C to obtain a slightly cloudy solution which is loaded on a column of 1 kg of silanized silica-gel (Merck) in H_2O. The column is developed with a linear gradient from 20% of CH_3CN in H_2O to 60% of CH_3CN in 0.001 N HCl in 20 h at the rate of 200 ml/h, while collecting 20 ml fraction which are monitored by HPLC. Those fractions which contain the amide of teicoplanin A_2 component 2 are pooled. Conveniently, also the fraction containing the amides of components 1-3 and 4 and 5 are pooled, respectively. Each solution is then concentrated to a small volume after adding suitable amounts of n-butanol to obtain a dry butanolic suspension from which the compounds of the title, as the free bases, precipitate as usual with ethyl ether. The addition of a small excess of 1N HCl or trifluoroacetic acid before concentration gives the corresponding hydrochlorides or trifluoroacetates, respectively.

Example 19

(Procedure A_6: reaction of an unprotected teicoplanin starting material with the α-amino group of Nω-nitro-arginine, methyl ester hydrochloride, followed by the cleavage of the protective nitro group of the resulting compound)

Preparation of compound 33

The first part of the reaction, starting from 16 g (~8 mmol) of teicoplanin A_2 and 12 mmol of Nω-nitro-arginine, methyl ester hydrochloride, is carried out according to the procedure A_2 described in Example 3, yielding 14 g of compound 105.

A solution of 14 g (~6.5 mmol) of this compound in 200 ml of 90% aqueous acetic acid is treated with 3.6 g (~55 g atom) of zinc powder under vigourous stirring at room temperature. The resulting suspension is stirred 30 min. at room temperature, then is it filtered. By adding ethyl acetate (~800 ml) to the filtrate, a powder (~13 g) separates which is collected by filtration and purified by reverse-phase column chromatography on 700 g of silanized silica-gel according tothe procedure described in Example 1, yielding 10.2 g of the title compound, as the free base (the yield of this reaction from compound 105 is about 75%).

Example 20

(Procedure A_7: reaction of a N^{15}-protected or unprotected teicoplanin starting material with the α-aminogroup of Nω-nitro-arginine, methyl ester or benzyl ester respectively, followed by subsequent deprotection of the N^{15}-t-BOC, or N^{15}-CBzO and benzyl protecting groups in acid medium according to procedure A_8, or by catalytic hydrogenation, according to procedure A_4, respectively, and final

Preparation of compounds 18-20, 22, 23, 30, 84 and 102

A suspension of 1 mmol of the selected amide of teicoplanin A_2 complex, or of antibiotic L 17054 or of antibiotic L 17056 in 50 ml of absolute trifluoroethanol (TFE) is stirred at 75°C for 12-16 h while bubbling dry HCl, then cooled to 10°C and left overnight at such a temperature. After adding 20 ml of ethyl ether, the crude compound of the title is recovered from the reaction mixture as dark yellow powder. Purification by column chromatography as reported in example 6c yields the pure compound.

EXAMPLE 14:

(Procedure F_1: transesterification and ester function hydrolysis of a compound of formula I)

Preparation of compound 17.

In a vessel protected with a soda-lime valve, a solution of 3 ml of methanolic 1 M KOH (85% commercial pellets) is added dropwise at room temperature to a stirred solution of 1.05 g (~0.7 mmol) of compound 16 (hydrochloride) in 60 ml of methanol. After 1 h, additional 0.75 ml of 1 M KOH in methanol is added and stirring is continued for 30 min (HPLC method b). Then the reaction mixture is cooled to about 5°C and 3.75 ml of 1 NHCl is added. The resulting solution is diluted with 200 ml of H_2O and 100 ml of CH_3CN. Silanized silica gel (0.063-0.2 mm, 5 g; Merck) and n-butanol (400 ml) are then added and the solvents are evaporated under vacuum at 40°C.

The residue is put at the top of a column containing 200 g of the same silanized silica gel prepared in H_2O. The column is developed with a linear gradient from 1 to 60% CH_3CN in H_2O in 20 h at the rate of 250 ml/h and then with a linear gradient from 60% CH_3CN in H_2O to 70% CH_3CN in 0.01 N HCl in 60 h at the rate of 150 ml/h. Fractions of 25 ml each are collected, assayed by HPLC and the compound 17 containing fractions (241-254) are pooled. 200 ml of n-butanol is added to the resulting solution which is then concentrated to a small volume under vacuum at 45°C to give a butanolic suspension. On adding ethyl ether a solid separates which is collected, washed with ether and dried in vacuo at 30°C overnight, yielding 0.795 g (~78%) of pure compound 17.

By essentially following this procedure, but using larger amounts of methanolic KOH and/or prolonging the reation time as necessary, the corresponding compound having a free carboxy function instead of the methoxycarbonyl function may be obtained.

EXAMPLE 15

(Procedure B_3: reaction of an unprotected or N^{15}-protected teicoplanin starting material with a NHR^1R^2 amine having a further amino group and/or further carboxy groups, all of which are protected.

Preparation of compounds 68 and 72

A solution of 3 ml (about 14 mmol) of DPPA in 25 ml of DMF is added dropwise to a stirred solution of 12 mmole of teicoplanin A_2 complex (in the case of the preparation of compound 68) or N^{15}-CBzO-deglucoteicoplanin (in the case of the preparation of compound 72), 13 mmole of N_ϵ-CBzO-Lysine methyl ester, hydrochloride and 24 mmol of triethylamine (TEA) in 225 ml of DMF, in 10 min while maintaining the tempeature at 0-5°C. After stirring 4 h at 0-5°C and 24 h at 20°C, the reaction mixture is poured into 1.5 l of ethyl ether and the precipitate which forms is collected by filtration and re-dissolved in 500 ml of a mixture methanol:water, 4:1 (v/v). The resulting solution is cooled to 10°C and 800 ml of n-butanol is added thereto under stirring. After adjusting the pH at about 8.3 (with 1N NaOH), the organic layer is separated, washed with 800 ml (2 × 400 ml) of water, then concentrated to a small volume (about 100 ml) under reduced pressure at 40°C overnight, yielding the title compound.

By essentially repeating the same procedure but starting from teicoplanin A_2 component 1, 2, 3, 4, or 5 the corresponding derivative of the single pure components is obtained.

EXAMPLE 16

(Procedure F_2: ester function hydrolysis of a compound of formula I)

Preparation of compounds 64, 69, 86 and 104

A solution of 5 g of K_2CO_3 in 500 ml of H_2O is added under stirring at room temperature to a solution of 4 mmol of compound 63 (for preparing compound 64), 68 (for preparing compound 69) 85 (for preparing compound 86) and 105 (for preparing compound 104), in 500 ml of a mixture methanol:water, 1:1 (v/v). After adding 750 ml of n-butanol, the resulting mixture is vigorously stirred for 36 h. The organic layer is separated, the aqueous phase is brought to pH 3.5 with 1N HCl and then extracted with 500 ml of n-butanol. The butanolic

room temperature for 2 h (HPLC, method a or b). On adding 800 ml of ethyl ether a solid separates which is rapidly collected, washed with ether and dried in vacuo at 40°C overnight, yielding the title compound (as the corresponding di-trifluoroacetate).

EXAMPLE 10: (Procedure D_1: transformation of an amide derivative of teicoplanin A_2 complex, of a single component thereof or of antibiotic L 17054 into the corresponding amide derivative of antibiotic L 17046)

Alternative preparation of compounds 13 to 15 and 50

A solution of 1 mmol of the proper amide of T-A2-complex or single component thereof or a amide of antibiotic L 17054 in 50 ml of a mixture tetrahydrofuran (THF) or dimethoxyethane (DME)-:conc. sulfuric acid (H_2SO_4), 80:20 (v/v) is stirred 12-48 h at room temperature (HPLC, method b). On adding 250 ml of ethyl ether a solid separates which is collected and re-dissolved in 300 ml of a mixture water:acetonitrile, 80:20 (v/v). The resulting solution is adjusted to about pH 8.4 with 0.1 n NaOH and extracted with 300 ml of n-butanol. The organic layer is separated, washed with 300 ml - (2*150 ml) of water and concentrated under vacuum at 40°C to a small volume after adding 3 ml of 1 N HCl. On adding ether a solid separates which is collected, washed with ether and dried overnight in vacuo at room temperature, yielding the title compound (as di-hydrochloride).

EXAMPLE 11 (Procedure D_2: transformation of an amide derivative of teicoplanin A_2 complex, of a single component thereof or of antibiotic L 17054 into the corresponding amide derivative of antibiotic L 17046)

Alternative preparation of compounds 13 -15 and 21

A suspension of 1 mmol of the selected amide of teicoplanin A_2 complex or a single component thereof or an amide of antibiotic L17054 in 100 ml of butanol 0.4 M (dry) HCl is stirred at 90°C for 4-6 h (HPLC, method b), then 200 ml of water and 100 ml of n-butanol are added under vigorous stirring at 10°C while adjusting the pH above at 8.4 with solid $NaHCO_3$. The organic layer is separated, washed with 200 ml (2*100 ml) of water and 3 ml of 1 N HCl is added thereto. The resulting butanolic solution is concentrated to a small volume. On adding ethyl ether a solid separates which is collected, washed with ether and dried overnight in vacuo at room temperature, yielding the compound of the title (as the corresponding di-hydrochloride).

For conveniently preparing compound 21 a slight modification of the above procedure is required which is:

the hydrolysis is conducted in butanolic 0.45 M HCl at about 65°C for 18 h, with stirring. The corresponding di-trifluoroacetate is isolated by substituting TFA for HCl in the treatment of the final butanolic solution as reported above.

EXAMPLE 12: (Procedure E_1: transformation of an amide derivative of a teicoplanin compound selected from teicoplanin A_2 complex, a single component thereof, antibiotic L17054 and antibiotic L 17046 into the corresponding amide of deglucoteicoplanin)

Preparation of compounds 18-20, 22, 23, 97, 99, 100, 101 and 103

A suspension of 1 mmol of the selected amide of teicoplanin A_2 complex, of antibiotic L 17054, or (13 and 15) of antibiotic L 17046 in 100 ml of 2-3 M (dry) HCl in n-butanol is stirred 6-8 h at about 75°C (HPLC, method b). Then, the solvent is evaporated under vacuum at 45°C, the residue is dissolved in 500 ml of a mixture water:methanol, 80:20 (v/v) and the resulting solution is adjusted to pH 8.5 with 1 N NaOH and extracted with 700 ml of a mixture n-butanol:ethyl acetate, 7:3 (v/v). The organic layer is suspended, washed with 500 ml of water (2*250 ml), 2 ml of TFA is added thereto and then the resulting mixture is concentrated to a small volume under vacuum. On adding ethyl ether a solid separates which is collected, washed with ether and dried in vacuo at 60°C overnight, yielding the compound of the title (as the di-trifluoroacetate).

When necessary, further purification of these compounds may be obtained e.g. by column chromatography according to the procedure described in example 3c.

EXAMPLE 13:

(Procedure E_2: transformation of an amide derivative of a teicoplanin compound selected from a teicoplanin A_2 complex, a single component thereof, antibiotic L 17054 and antibiotic L 17046 into the corresponding amide of deglucoteicoplanin)

Preparation of compounds 11, 14, 18, 19, 20, 21, 23, 24 25, 31, 52, 53, 78, 79, 83 and 94

a) preparation of the N-tert-butoxycarbonyl protected teicoplanin starting material (N-t-BOC-ST)

A mixture of 4 mmol of the selected teicoplanin starting material 2 ml (14.5 mmol) of TEA and 2 g (~7 mmol) of tert-butyl 2,4,5-trichlorophenylcarbonate in 100 ml of DMF is stirred 24 h at room temperature. On adding ether (900 ml) a solid separates which is collected and re-dissolved in a mixture (1 l) water:methanol 7:3. The resulting solution is brought to pH 3.5 with 1 N HCl, then extracted with ether (500 ml). The aqueous layer is extracted again with n-Butanol (1 l). The butanolic layer is washed with water (2 x 500 ml) and concentrated to a small volume under vacuum at 35°C. By adding ethyl ether a solid is precipitated which is collected, washed with ether and dried in vacuo at 40°C overnight, yielding (the yields are always higher than 90%) the N-t-BOC protected teicoplanin starting material pure enough (HPLC titre > 90%, method c) for the next step.

b) preparation of the N-t-BOC derivative of the teicoplanin amide compound

The condensation of the above obtained N-t-BOC protected teicoplanin starting material with the selected amine is carried out in DMF (HPLC, method c) in the presence of DPPA under the same conditions described in the example 1. Like in the case of the N-CBzO-teicoplanin amide (see example 4 b), the crude N-t-BOC-teicoplanin amide obtained from the reaction mixture after precipitation with ethyl ether is pure enough for use in the deprotection step.

c) preparation of the teicoplanin amide derivative of the title

A solution of 1 mmol of N-t-BOC-teicoplanin amide in 40 ml of 100% trifluoroacetic acid (TFA) is stirred 10-20 min at 5°C, afterwards the solvent is evaporated under vacuum at 25°C. The oily residue is triturated with ether, then collected and re-dissolved in 150 ml of methanol. Silanized silica gel (0.063-0.2 mm 5g Merck) is added and the solvent is evaporated under vacuum at 40°C. The residue is put at the top of a column containing the same silanized silica gel (150 g) prepared in the mixture water:acetonitrile 95:5 (v/v). Column chromatography is carried out substantially according to the procedure described in xample 4 c. More particularly, the column is developed with a linear gradient elution from 5% CH_3CN in 0.001 N HCl to 30% CH_3CN in H_2O in the case of compound 9, with a linear gradient elution from 10% CH_3CN in 0.001 N HCl to 40% CH_3CN in H_2O in the case of compound 14 and with a linear gradient from 20% CH_3CN in 0.001 N HCl to 55% CH_3CN in water in the case of compound 22. The flow rate is 120 ml/h and the time is 15 h. Fractions of 12 ml are collected, monitored by HPLC and worked up substantially as already described in example 4c.

Fractions containing the pure compounds of the title are pooled and to the resulting solution n-butanol (v/v) and 1 N HCl (2 ml) are added. After concentration to a small volume under vacuum at 40°C the title compound is obtained (as the corresponding di-hydrochloride, except for compound no. 25 which is recovered as mono-hydrochloride) by precipitating with ethyl ether from the butanolic phase, washing and drying overnight in vacuo at 40°C.

EXAMPLE 8:

Preparation of the trifluoroacetate salts of teicoplanin compound amides 18-25.

A teicoplanin compound amide (amides 18 - 25) is dissolved (1 g in 300 ml) in a mixture water:acetonitrile, 8:2 (v/v). The resulting solution is brought to pH 8.5 with 0.1 n NaOH and extracted - (v/v) with n-butanol. The organic layer is separated, washed with water (v/v) and concentrated to a small volume. On adding ether, the solid which separates is collected, washed with ether and dried overnight in vacuo at 35°C, yielding the corresponding free base which is re-dissolved in TFA (1 g in 10 ml) and precipitated with ethyl ether (100-200 ml). After collecting the solid by filtration, washing with ether and drying in vacuo 24 h at room temperature, the title compounds are obtained (18 -24, di-trifluoroacetates and 25 trifluoroacetate).

EXAMPLE 9: (Procedure C: transformation of an amide derivative of teicoplanin A_2 complex or teicoplanin A_2 single components 1, 2, 3, 4 or 5 into the corresponding amide derivative of antibiotic L 17054)

Preparation of compounds 7 to 12, 28, 29 and 41 to 49

A solution of 1 mmol of the selected amide of teicoplanin A_2 complex or of a single component thereof in 200 ml of 90% aqueous TFA is stirred at

Preparation of compound 36, 37, 39, 71 and 90.

The procedure of the first part of Example 1 - (procedure A_1) is ss ntially followed.

Once the condensation product bearing either th additional amino or the carboxy functions protected is obtained, it is deprotected by catalytic hydrogenation using Palladium on carbon as described in the second part of the Example 6 below, procedure B_1).

EXAMPLE 5:(Procedure A_2: reaction of an unprotected teicoplanin starting material with a HNR^1R^2 amine having a further amino group and/or further carboxyl groups which are protected and its subsequent deprotection in acidic medium).

Preparation of compounds 48 and 57.

The procedure of the first part of Example 1, - (procedure A_1) is essentially followed.

The selected amine is in this case an amine compound bearing further carboxyl functions which are protected by groups removable under anhydrous acid conditions such as glutamic acid di-butyl ester. Once the condensation product bearing the protected carboxy functions is obtained, it is deprotected in an acid medium consisting of anhydrous trifluoroacetic (as described in the second part of Example 7 below, procedure B_2).

EXAMPLE 6: (Procedure B_1: reaction of a N-protected teicoplanin starting material and a selected amine followed by deprotection by catalytic hydrogenation).

Preparation of compounds 9, 13, 22, 54, 61 and 73

a) preparation of the N-benzyloxycarbonyl protected starting material (NCBzO-ST)

A solution of 0,45 ml of benzyl chloroformate in 10 ml of dry acetone is added dropwise, while cooling 0-3°C, to a stirred solution of 2 mmol of the selected teicoplanin starting material and 0.5 g of $NaHCO_3$ in 150 ml of a mixture acetone:water, 2:1 (v/v). After about 30 min., 500 ml of water is added and the resulting solution is extracted with 500 ml of ethyl ether. The aqueous layer is adjusted to about pH 3.5 with 1 HCl and then is extracted with 500 ml of n-butanol. The organic layer is separated, washed with 400 ml of water (2 x 200 ml), then concentrated to a small volume at 45°C under vacuum. On adding ethyl ether a solid separates which is collected, washed with ether and dried at room temperature in vacuo overnight, yielding the N-CBzO derivative of the teicoplanin starting material having a purity (HPLC titre > 90%, method c) enough for the next step (yield > 80%)

b) preparation of the N-CBzO derivative of th teicoplanin amide compound

The condensation of the above obtained N-benzoyloxycarbonyl starting material with the selected amine is carried out in DMF (HPLC, method c) in the presence of DPPA under the same r action conditions as described in example 1. The N-CBzO-teicoplanin amide compound is obtained as a solid which precipitates from the reaction mixture by adding ethyl ether.

c) preparation of the teciplanin amide derivativ of the title

The above obtained crude N-CBzO-teicoplanin amide (1 g) is dissolved in a mixture (100 ml) of methanol:0.1 N hydrochloric acid, 7:3 (v/v) and the resulting solution is hydrogenated at room temperature and pressure in the presence of (0.5 g) 5% Pd/C. The reaction is generally completed within 1 h (HPLC, method c). The reaction mixture is filtered and to the clear filtrates a mixture of silanized silica gel (0.063-0.2 mm; 4 g Merck) and n-butanol (60 ml) is added. The solvents are then evaporated under vacuum at 45°C and the residue is applied to a chromatographic column containing the same type of silanized silica gel (100 g) prepared in a mixture water:acetonitrile, 95:5 (v/v).

The column is developed with a linear-gradient elution from 5% (compound 9), 10% (compound 13) and 20% (compound 22) CH_3CN in 0.001 N HCl to 30%, 40% and 55%, respectvely, CH_3CN in H_2O in 15 h at the rate of 120 ml/h. Fractions of 12 ml each are collected and assayed by HPLC. Fractions containing the pure compounds of the title are pooled and to the resulting solution n-butanol (v/v) and 1 N HCl (2 ml) are added. After concentration to a small volume under vacuum at 40°C, the title compounds are obtained (as the corresponding dihydrochloride) by precipitating with ethyl ether from the butanolic phase, washing and drying overnight in vacuo at 40°C.

EXAMPLE 7: (Procedure B_2 : reaction of an N-protected teicoplanin starting material with a selected amine followed by deprotective acid hydrolysis).

80% CH_3CN in 0.01 N HCl in 20 h at the rate of 2590 ml/h.

Fractions of 25 ml are collected and monitored by HPLC. Fractions containing the pure compound of the title are pooled and th resulting solution is brought to pH 8,5 with 1 N NaOH, and an equal volume (v/v) of water is then added. This mixture is then extracted with butanol (v/v) and the organic layer is separated, washed with water and concentrated under vacuum at 40°C until most of the water is eiliminated. The cloudy butanolic solution is filtered, ethyl acetate (0.5 v/v, i.e. half a volume of solvent per volume of solution) is added and the suspension (or cloudy solution) which formes is extracted with water (0.5 v/v). The organic layer is concentrated to a small volume, ethyl ether is added and the solid which separates is collected, washed with ether, then dried in vacuo at 50°C overnight, yielding the title compound as the corresponding free base which is then dissolved in methanol (in general 1 g in 50 -100 ml). Glacial acetic acid (0.5 ml per gram of the free base) is added and the resulting solution is stirred a few minutes at room temperature. By adding ethyl ether (300-500 ml), a solid separates which is collected, washed with ether (100 ml) and dried overnight at room temperature, yielding the title compounds as the corresponding monoacetate salt.

EXAMPLE 2: (Procedure A_2 : reaction of unprotected teicoplanin starting material with the selected amine and preparation of the hydrochloride salt of the final compound)

Preparation of compounds no. 13, 18, 76, 77, 80, 81, 89 and 91

The reaction between teicoplanin A_2 complex and the selected amine is conducted as described in example 1. Once the crude product of the title is precipitated with ethyl ether and separated as a solid, it is suspended in methanol (about 1 g of substance in 100 ml of solvent). Water is added - (v/v) and the resulting solution (or suspension) is brought to pH 2,5 with 1 N HCl. Then silanized silica gel (0.063-0.2 mm 5 g per gram of crude product -Merck) and n-butanol (200 ml) are added. The resulting suspension is stirred a few minutes at room temperature, afterwards the solvents are completely evaporated and the residue is put at the top of a chromatographic column containing the same kind of silanized silica gel (100 g), equilibrated with the mixture water:acetonitrile, 95:5 (v/v). The column is developed with linear gradient elutions from 5% to 40% (in the case of compound 13) or 15% ot 60% (in the case fo compound 18) of CH_3CN in 0.001 N HCl, in 20 h at the rate of 100 ml/h. Fractions of 10 ml are collected and assayed by HPLC (method b). Fractions containing the title compound are pooled and concentrated under vacuum at 45°C and by adding suitable amounts of n-butanol a final water-free butanolic cloudy solution (about 200 ml) is obtained. After adding 1 N HCl (0,2 ml) the solution is concentrated to a small volume under vacuum at room temperature (below 25°). Precipitation with ethyl ether, washing with ether and drying in vacuo at 40°C overnight, yield the title compound (as the corresponding di-hydrochloride).

EXAMPLE 3: (Procedure A_3: reaction of an unprotected teicoplanin starting material with an acid addition salt of the selected amine in the presence of a base)

Preparation of compound Nos. 16, 38, 75, 85, 92 and 105

A solution of 0,6 ml (2,8 mmol) of DPPA in 2 ml of DMF is added to a stirred solution of 2,8 g (2 mmol) of antibiotic L 17046 and 0,6 g(4,2 mmol) of glycine ethyl ester, hydrochloride, in 100 ml of DMF at 0-5°C. After adding 1.1 ml (8 mmol) of triethylamine (TEA) the reaction mixture is stirred 2 h at 5°C and overnight at room temperature. The reaction course is monitored by HPLC (method b). The resulting solution is poured into 500 ml of ethyl ether and the precipitate which forms is collected and re-dissolved in 500 ml of a mixture water:acetonitrile, 7:3 (v/v) while adjusting the pH at 2.3 with 1 N HCl. After adding 600 ml of n-butanol and 200 ml of water, the mixture is brought to pH 8.2 with 1 N NaOH under vigorous stirring. The organic layer is separted, washed with 400 ml (2 x 200 ml) of water, then concentrated to a small volume (about 50 ml) at 50°C under vacuum. By adding ethyl ether (200 ml) a solid (the title compound as the free base) separates which is collected and re-dissolved in 200 ml of methanolic 0.02 M HCl. By adding ethyl ether (500 ml) a precipitate separates which is collected, washed with ether and dried in vacuo at 40°C overnight, yielding 1.62 g of compound 16 as the corresponding hydrochloride).

EXAMPLE 4:(Procedure A_4: reaction of an unprotected teicoplanin starting material with a HNR^1R^2 amine having a further amino group and/or further carboxyl groups, all of which are protected, and its subsequent deprotection by catalytic hydrogenation).

compounds of the present invention may also be prepared in suitable forms for absorption through the mucous membranes of the nose and throat or bronchial tissues and may conveniently take the form of liquid sprays or inhalants, lozenges, or throat paints.

For medication of the eyes or ears, the preparation may be presented in liquid or semi-liquid form. Topical applications may be formulated in hydrophobic or hydrophilic bases as ointments, creams, lotions, paints, or powders.

For rectal administration the compounds of the invention are administered in the form of suppositories admixed with conventional vehicles, such as, for example, cocoa butter, wax, spermaceti or polyethylenglycols and their derivatives.

Compositions for injection may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution at the time of delivery with a suitable vehicle, such as sterile water.

The amount of active principle to be administered depends on various factors such as the size and conditions of the subject to be treated, the route and frequency of administration, and the causative agent involved.

The compound of the invention are generally effective at a dosage comprised between about 0.5 and about 30 mg of active ingredient per Kg of body weight, preferably divided in 2 to 4 administrations per day. Particularly desirable compositions are those prepared in the form of dosage units containing from about 20 to about 300 mg per unit.

Representative examples of preparation of pharmaceutical compositions are as follows:

A parenteral solution is prepared with 100 mg of compound No 3 dissolved in 2 ml of sterile water for injection. A parenteral solution is prepared with 250 mg of compound N 19 hydrochloride dissolved in 3 ml of sterile water for injection.

A topical ointment is prepared with 200 mg of compound No 19.

3.6 g of polyethylene glycol 4000 U.S.P.

6.2 g of polyethylene glycol 400 U.S.P.

Besides their activity as medicaments, the compounds of the present invention can be used as animal growth promoters.

For this purpose, one or more of the compounds of the invention is administered orally in a suitable feed. The exact concentration employed is that which is required to provide for the active agent in a growth promotant effective amount when normal amounts of feed are consumed. The addition of the active compounds of the invention to animal feed is preferably accomplished by preparing an appropriate feed premix containing the active compounds in an effective amount and incorporating the premix into the complete ration.

Alternatively, an intermediate concentrate or feed supplement containing the active ingredient can be blended into the feed.

The way in which such feed premixes and complete rations can be prepared and administered are described in reference books (such as "Applied Animal Nutrition", W.H. Freedman and Co., S. Francisco, USA, 1969 or "Livestock Feeds and Feeding", O and B Books, Corvallis, Oregon, USA, 1977) and are incorporated herein by reference.

EXAMPLE 1: (Procedure A, reaction of unprotected teicoplanin starting material with the selected amine and preparation of the acetate salt of the final compound)

Preparation of compounds no. 1 to 6, 26, 34, 35, 82, 87, 88 and 95

To a stirred solution of 1 mmol of teicoplanin A_2 complex prepared as described in US 4239751 and 2 mmol of the selected amine in 20 ml of dimethylformamide (DMF), a solution of 1.1 mmol of diphenylphosphorylazide (DPPA) in 5 ml of DMF is added dropwise in 10 min while cooling to 0-5°C. The reaction mixture is stirred for about 6 h at 5°C and overnight at room temperature, afterwards a solution of 0.5 mmol of DPPA in 2.5 ml of DMF is added dropwise at 0-5°C. Stirring is continued at room temperature for additional 24 h, then 125 ml of ethyl ether is added and the solid which separates is collected, washed with 100 ml of ether and re-dissolved in 100 ml of a mixture water:acetonitrile, 8:2 (v/v) adjusted at pH 2,5 with 1 n HCl. The resulting solution is applied to a chromatographic column, prepared with 250 g of silanized silica gel (0,063-0,2 mm; Merck) pre-equilibrated with a mixture water:acetonitrile 8:2 - (v/v). The column is developed with a linear gradient lution from 20% CH_3CN in 0.001 N HCl to

TABLE X (continued)

Compound	ED_{50} (mg/kg) Route of administration	
	os.	s.c
87	112	0.12
88	300	0.18
89	> 300	0.08
90	89.6	0.08
91	139	0.08
92	N.T.	N.T.
93	> 300	1.25
94	> 300	1.25
95	140	0.09
96	90	0.07
97	> 300	0.54
99		
100		
101		
102		
103	N.T.	N.T.
104	> 300	0.2
105	> 300	0.13

In view of the above reported antimicrobial activity, the compounds of the present invention can effectively be employed as the active ingredient of antimicrobial preparations used in human and veterinary medicine for the prevention and treatment of infectious diseases caused by pathogenic bacteria which are susceptible to said active ingredients.

In such treatments, these compounds may be employed as such or in the form of mixtures in any proportion.

The compounds of the present invention can be administered orally, topically or parenterally wherein however, the parenteral administration is preferred. Depending on the route of administration, these compounds can be formulated into various dosage forms. Preparations for oral administration may be in the form of capsules, tablets, liquid solutions or suspensions. As known in the art the capsules and tablets may contain in addition to the active ingredient, convention excipients such as diluents, e.g. lactose, calcium phosphate, sorbitol and the like, lubricants, e.g. magnesium stearate, talc, polyethylene glycol, binding agents, e.g. polyvinylpyrrolidone, gelatin, sorbitol, tragacanth, acacia, flavoring agents, and acceptable disintegrating and wetting agents. The liquid preparations generally in the form of aqueous or oily solutions or suspensions, may contain conventional additives such as suspending agents. For topical use the

TABLE X (continued)

Compound	ED_{50} (mg/kg) Route of administration	
	os.	s.c
26	220	0.08
27	90	0.06
28	> 300	1.6
29	> 300	2.2
30	> 300	> 10
31	> 300	2.9
33		
60		
66	> 300	5
70	90	0.15
71	72	0.08
73	> 300	0.81
74	> 300	0.3
75	139	0.08
76	140	0.1
77	> 300	0.18
78	> 300	1.4
79	> 300	1.25
80	300	0.14
81	90	0.1
82	173	0.07
83	> 300	0.46
84	> 300	1.65
85	300	0.10
86	300	0.23

TABLE X

Compound	ED_{50} (mg/kg) Route of administration	
	os.	s.c
1	70.7	0.047
2	89.6	0.046
3	~ 300	0.099
4	~ 300	0.08
5	173	0.062
6	115	< 0.03
7	> 300	0.81
8	> 300	0.3
9	> 300	0.3
10	> 300	1.6
11	> 300	0.41
12	> 300	0.95
13	> 300	2.2
14	N.T.	N.T.
15	> 300	2.2
16	> 300	5
17	> 300	~ 7
18	140	0.31
19	> 300	0.18
20	> 300	0.72
21	> 300	2.2
22	> 300	1.6
23	> 300	0.95
24	> 300	0.72
25	> 300	1.02

TABLE IX (continued)

Microorganism	Compound MIC (μg/ml)						
	100	101	102	103	104	105	
S.aureus ATCC 6538	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	
S.aureus Tour	0.06	0.06	0.06	2	0.25	0.12	
S.epidermidis ATCC 12228	0.06	0.06	0.06	0.5	1	0.12	
S.pyogenes C 203	0.06	0.06	0.06	0.5	0.06	0.06	
S.pneumoniae UC 41	0.12	0.12	0.06	0.5	0.06	0.06	
S.faecalis ATCC 7080	0.12	0.12	0.12	1	0.25	0.12	
E.coli SKF 12140	8	16	4	64	> 128	> 128	
Proteus vulgaris X 19H	128	128	64	> 128	> 128	> 128	
Pseudomonas aeruginosa ATCC 10145	64	128	64	128	> 128	> 128	

The ED_{50} values (mg/Kg) of representative compounds of the invention in vivo tests in mice experimentally infected with S.pyogenes L 49 according to the procedure described by V. Arioli et al., Journal of Antibiotics 29, 511 (1976) are reported in table X below:

TABLE IX (continued)

Microorganism	Compound					
	93	94	95	96	97	99
	MIC (µg/ml)					
S.aureus ATCC 6538	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.
S.aureus Tour	0.06	0.06	0.12	0.12	0.12	0.06
S.epidermidis ATCC 12228	0.06	0.06	0.06	0.06	0.06	0.06
S.pyogenes C 203	0.06	0.06	0.06	0.06	0.06	0.06
S.pneumoniae UC 41	0.06	0.06	0.06	0.12	0.12	0.12
S.faecalis ATCC 7080	0.12	0.12	0.12	0.12	0.12	0.12
E.coli SKF 12140	8	4	> 128	> 128	8	8
Proteus vulgaris X 19H	64	32	> 128	> 128	32	32
Pseudomonas aeruginosa ATCC 10145	64	16	128	> 128	32	32

TABLE IX (continued)

Microorganism	Compound 87	88	89	90	91	92
	MIC (µg/ml)					
S.aureus ATCC 6538	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.
S.aureus Tour	0.12	0.12	0.12	0.12	0.12	0.5
S.epidermidis ATCC 12228	0.12	0.12	0.12	0.12	0.12	0.5
S.pyogenes C 203	0.6	0.6	0.6	0.6	0.6	0.6
S.pneumoniae UC 41	0.06	0.12	0.06	0.06	0.06	0.12
S.faecalis ATCC 7080	0.12	0.12	0.12	0.12	0.12	0.12
E.coli SKF 12140	> 128	> 128	> 128	> 128	> 128	> 128
Proteus vulgaris X 19H	> 128	> 128	> 128	> 128	> 128	> 128
Pseudomonas aeruginosa ATCC 10145	> 128	> 128	> 128	> 128	> 128	> 128

TABLE IX (continued)

Microorganism	Compound 81	82	83	84	85	86
	MIC (µg/ml)					
S.aureus ATCC 6538	N.T.	N.T.	N.T.	N.T.	N.T	N.T
S.aureus Tour	0.12	0.12	0.12	0.12	0.25	0.12
S.epidermidis ATCC 12228	0.06	0.06	0.06	0.06	0.12	0.12
S.pyogenes C 203	0.06	0.06	0.06	0.12	0.06	0.12
S.pneumoniae UC 41	0.12	0.06	0.06	0.12	0.06	0.12
S.faecalis ATCC 7080	0.12	0.12	0.12	0.12	0.12	0.25
E.coli SKF 12140	> 128	> 128	8	64	> 128	> 128
Proteus vulgaris X 19H	> 128	> 128	64	> 128	> 128	> 128
Pseudomonas aeruginosa ATCC 10145	> 128	> 128	32	> 128	> 128	> 128

TABLE IX (continued)

Microorganism	Compound					
	75	76	77	78	79	80
	MIC (μg/ml)					
S.aureus ATCC 6538	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.
S.aureus Tour	0.12	0.12	0.12	0.06	0.06	0.12
S.epidermidis ATCC 12228	0.25	0.06	0.12	0.06	0.06	0.06
S.pyogenes C 203	0.06	0.06	0.06	0.06	0.06	0.06
S.pneumoniae UC 41	0.06	0.06	0.06	0.12	0.06	0.12
S.faecalis ATCC 7080	0.12	0.12	0.12	0.12	0.12	0.12
E.coli SKF 12140	> 128	> 128	> 128	8	4	> 128
Proteus vulgaris X 19H	> 128	> 128	> 128	64	32	> 128
Pseudomonas aeruginosa ATCC 10145	> 128	> 128	> 128	32	64	> 128

TABLE IX (continued)

Microorganism	Compound 60	66	70	71	73	74
	MIC (μg/ml)					
S.aureus ATCC 6538	N.T	N.T.	N.T.	N.T.	N.T.	N.T.
S.aureus Tour	0.25	0.12	0.12	0.12	0.06	4
S.epidermidis ATCC 12228	0.06	0.012	0.06	0.12	0.06	4
S.pyogenes C 203	0.12	0.12	0.06	0.06	0.12	0.06
S.pneumoniae UC 41	0.12	0.12	0.06	0.06	0.06	0.12
S.faecalis ATCC 7080	0.25	0.5	0.12	0.12	0.12	0.25
E.coli SKF 12140	32	> 128	> 128	> 128	4	> 128
Proteus vulgaris X 19H	128	> 128	> 128	> 128	32	> 128
Pseudomonas aeruginosa ATCC 10145	64	> 128	> 128	> 128	32	> 128

TABLE IX (continued)

Microorganism	Compound 26	27	28	29	30	31	33
	MIC (μg/ml)						
S.aureus ATCC 6538	N.T	N.T	N.T	N.T.	N.T.	N.T.	N.T.
S.aureus Tour	1	0.5	1	2	4	0.5	0.12
S.epidermidis ATCC 12228	0.25	0.25	0.12	0.25	0.12	0.063	0.012
S.pyogenes C 203	0.06	0.06	0.5	0.5	1	0.12	0.06
S.pneumoniae UC 41	0.12	0.12	0.5	1	2	0.25	0.06
S.faecalis ATCC 7080	0.12	0.12	2	2	2	0.25	0.12
E.coli SKF 12140	> 128	> 128	> 128	> 128	> 128	64	> 128
Proteus vulgaris X 19H	> 128	> 128	> 128	> 128	> 128	> 128	> 128
Pseudomonas aeruginosa ATCC 10145	> 128	> 128	> 128	> 128	> 128	> 128	> 128

TABLE IX (continued)

Microorganism	Compound 21	22	23	24	25
	MIC (μg/ml)				
S.aureus ATCC 6538	0.06	N.T	0.06	0.06	0.12
S.aureus Tour	0.12	0.12	0.12	0.12	0.12
S.epidermidis ATCC 12228	0.016	0.016	0.032	0.063	0.016
S.pyogenes C 203	0.12	0.06	0.12	0.06	0.12
S.pneumoniae UC 41	0.12	0.12	0.12	0.06	0.12
S.faecalis ATCC 7080	0.12	0.12	0.12	0.12	0.12
E.coli SKF 12140	16	8	16	32	16
Proteus vulgaris X 19H	128	64	64	> 128	64
Pseudomonas aeruginosa ATCC 10145	64	64	32	> 128	64

TABLE IX (continued)

Microorganism	Compound 16	17	18	19	20
	MIC (μg/ml)				
S.aureus ATCC 6538	0.5	N.T.	0.06	0.12	0.6
S.aureus Tour	1	0.5	0.12	0.12	0.25
S.epidermidis ATCC 12228	0.12	0.06	0.016	0.032	0.063
S.pyogenes C 203	0.25	0.25	0.06	0.06	0.06
S.pneumoniae UC 41	1	2	0.12	0.12	0.12
S.faecalis ATCC 7080	1	0.5	0.12	0.12	0.25
E.coli SKF 12140	128	> 128	8	8	8
Proteus vulgaris X 19H	> 128	> 128	16	32	32
Pseudomonas aeruginosa ATCC 10145	> 128	> 128	32	32	64

TABLE IX (continued)

Microorganism	Compound 11	12	13	14	15
	MIC (µg/ml)				
S.aureus ATCC 6538	N.T.	0.5	0.12	N.T.	N.T.
S.aureus Tour	0.5	2	0.12	0.5	0.12
S.epidermidis ATCC 12228	0.25	0.12	0.06	0.12	0.06
S.pyogenes C 203	0.12	0.5	0.12	0.5	0.25
S.pneumoniae UC 41	00.5	1	0.25	1	0.25
S.faecalis ATCC 7080	0.5	2	0.25	0.5	0.5
E.coli SKF 12140	> 128	> 128	64	> 128	128
Proteus vulgaris X 19H ATCC 881	> 128	> 128	> 128	> 128	> 128
Pseudomonas aeruginosa ATCC 10145	> 128	> 128	> 128	> 128	> 128

TABLE IX (continued)

Microorganism	Compound 6	7	8	9	10
	MIC (μg/ml)				
S.aureus ATCC 6538	0.12	0.25	0.12	0.5	N.T.
S.aureus Tour	0.25	0.5	1	2	1
S.epidermidis ATCC 12228	0.12	0.12	0.06	0.06	0.008
S.pyogenes C 203	0.06	0.12	0.12	0.12	0.12
S.pneumoniae UC 41	0.12	0.5	0.5	0.5	0.5
S.faecalis ATCC 7980	0.06	1	0.5	0.5	1
E. coli SKF 12140	> 128	> 128	> 128	> 128	> 128
Proteus vulgaris X 19H ATCC 881	> 128	128	> 128	> 128	> 128
Pseudomonas aeruginosa ATCC 10145	> 128	> 128	> 128	> 128	> 128

TABLE IX

Microorganism	Compound 1	2	3	4	5
	MIC (µg/ml)				
S.aureus ATCC 6538	0.12	0.12	0.25	N.T.	N.T.
S.aureus Tour	0.25	0.5	0.5	0.5	0.25
S.epidermidis ATCC 12228	0.06	0.12	0.06	0.12	0.06
S.pyogenes C 203	0.06	0.06	0.06	0.06	0.06
S.pneumoniae UC 41	0.06	0.06	0.06	0.12	0.12
S.faecalis ATCC 7980	0.12	0.12	0.12	0.12	0.12
E. coli SKF 12140	> 128	> 128	> 128	> 128	> 128
Proteus vulgaris X 19H ATCC 881	> 128	> 128	> 128	> 128	> 128
Pseudomonas aeruginosa ATCC 10145	128	> 128	> 128	> 128	> 128

TABLE VIII

(Isoelectric point (pI) determined by IEF techique)

Compound	pI
71	9.0
74	7.8
75	7.8
77	8.1
78	8.1
81	9.0
82	8.9
83	8.9
84	7.8
85	7.7
86	5.8
87	9.1
89	7.7
92	7.8
100	9.0
101	9.1
104	5.8
105	7.8

The antibacterial activity of the compounds of the invention can be demonstrated invitro by means of standard agar-dilution tests.

Isosensitest broth (Oxoid) and Todd-Hewitt broth - (Difco) are used for growing staphylococci and streptococci, respectively. Broth cultures are diluted so that the final inoculum is about 10^4 colony forming units/ml (CFU/ml). Minimal inhibitory concentration (MIC) is considered as the lowest concentration which shows no visible growth after 18-24 h incubation at 37°C. The results of the antibacterial testing of representative compounds of formula I are summarized in Table IX below:

TABLE VIII

(Isoelectric point (pI) determined by IEF techique)

Compound	pI
28	7.8
29	7.9
31	7.9
34	8.7
35	8.6
36	5.8
37	8.5
38	5.8
39	4.2
40	5.6
43	8.7
44	8.7
45	5.7
46	8.6
47	7.8
48	4.1
51	8.5
56	5.8
57	4.2
62	8.6
63	8.4
64	5.7
65	5.8
66	4.2
67	5.6
68	7.8
69	5.8

TABLE VIII

(Isoelectric point (pI) determined by IEF techique)

Compound	pI
1	8.9
2	8.8
3	8.7
4.	8.0
5	8.8
6	7.9
7	8.9
8	8.8
9	8.7
10	8.0
11	8.8
12	7.9
13	8.9
14	8.0
15	8.8
16	7.8
17	7.8
18	8.9
19	8.7
20	8.7
21	7.9
22	8.8
23	8.0
25	7.8
26	7.8
27	7.8

Ampholine carrier ampholytes (40% w/v) were purchased from LKB Produketer AB, Bromma, Sweden. Acrylamide, N,N'-methylenbisacrylamide - (BIS), N,N,N',N'-tetramethylethylenediamine - (TEMED) and ammonium persulfate were from Bio Rad Laboratorie, Richmond, California, USA. Glycerol and Antibiotic agar N. 1 (Grove and Randall medium N. 1) were from E. Merck Darmsatadt FRG. Gel fix polyester sheets were purchased from Serva Feinbiochemica Heidelberg. Phenolindo (2,6-dichlorophenol) came from BDH Chemicals Ltd. Poole, England.

Isoelectring focusing

IEF was made on gel slab using a LKB Multiphor 2117 cell and a Bio-Rad Power Supply Model 1420A. Slabs of 24.5x11.5 cm and 1 mm thickness were prepared on a sheet of Gel Fix.

Polyacrylamide gels with a concentration of 8% T and with a cross-linkage of 4% C (30% T stock solution was prepared by dissolving 28.8 g of acrylamide and 1.2 g of bis-acrylamide in 100 ml distilled water), glycerol, 3.5% v/v, 2% Ampholine, 0.05% ammonium persulphate as catalyst and 0.05% Temed as accelerator.

The carrier ampholite composition for 35 ml gelling solution was as follows:

1) pH 3.5-10: 1.6 ml Ampholine 3.5-10, 0.05 ml Ampholine 4-6, 0.05 ml Ampholine 7-9 and 0.05 ml Ampholine 8-9.5.

2) pH 2.5-6: 0.4 ml Ampholine 2.5-4, 1.1 ml Ampholine 4-6, 0.2 ml Ampholine 3-10.

3) pH 7-10: 0.5 ml Ampholine 7-9, 0.8 ml Ampholine 8-9.5, 0.4 ml Ampholine 9-11.

The electrode solutions, as recommended by LKB for the respective pH range, were:

pH range	Anode	Cathode
3.0-10	1M H_3PO_4	1M NaOH
2.5-6	1M H_3PO_4	0.5% Ampholine 5-7
7.0-10	0.1% Ampholine 7-9	1M NaOH

Experimental conditions

The gel was cooled to 4°C with the aid of a LKB 2209 refrigerated contant temperature circulator. After prefocusing for 30 min. at 5 W, the samples (20µl containing 0.2 to 2.5 µg of antibiotic) were loaded into the slot at the cathodic side.

Electrofocusing was performed using 10 W constant power and was completed after 3-3.1/2 hours with a final potential of 1400 V.

pI determination

The pH values were determined by dividing a portion of the gel into 1 cm sections, and eluting the individual pieces at room temperature with 1 ml of 10 mM CKI prior to pH readings.

The isolectric point of each antibiotic was determined by interpolation on a curve obtained by plotting pH values versus the distance from the anode. The results obtained performing at the two separate ranges of pH are presented in Table VIII below.

Microbiological development

The antibiotics were revealed by bioautography. Polyacrylamide gel was places on a 3 mm layer of agar medium N. 1 inoculated with 1% of Bacillus subtilis ATCC 6633 nspore (0.5 OD at 600 nm). After 10 mi. the gel was removed and the plate was incubated overnight at 37°C and examined for inhibition zones. The contrast between the area of lysis and that of bacterial growth was enhanced by use of Phenolindo(2,6-dichlorophenol)-1% w/v (odixation-reduction indicator).

TABLE VII (continued)

^{1}H-NMR spectra (δ, ppm) in DMSO-d_6

Compound	
101	1.29, 1.46, 1.61, 2.98, 3.18 (alkylamino groups); 2.70 ($N-CH_3$); 4.05-5.73 (peptidic CH's); 6.22-7.93 (aromatic protons)
102	1.21-1.53, 2.76, 3.12 (alkylamino groups); 4.11-5.63 (peptidic CH's); 6.20-7.93 (aromatic protons)
103	3.98, 3.37, 1.22-1.85, 0.85 (alkylamino and acyl groups); 4.10-5.65 (peptidic CH's); 6.22-7.90 (aromatic protons)
104	0.84, 1.16, 1.49, 2.04 (acyl chain); 1.88 (acetylglucosamine); 3.07, 1.79 1.24 (alkylamino groups); 3.49 (mannose); 6.29-7.92 (aromatic protons)
105	0.84, 1.17, 1.52, 2.06 (acyl chain); 1.89 (acetylglucosamine); 3.08, 1.78, 1.23 (alkylamino groups); 3.70 (CH_3-ester); 3.48 (mannose); 6.30-7.93 (aromatic protons)

Isoelectric point (pI)

The isoelectrofocusing (IEF) technique coupled with bioautography detection has been used for the determination of the pI of representative compounds of the invention using the following materials:

TABLE VII (continued)

^{1}H-NMR spectra (δ, ppm) in DMSO-d_6

Compound	
96	0.85, 1.15, 1.33, 2.03 (acyl chain); 1.87 (acetylglucosamine); 3.05, 1.41 (alkylamino groups); 3.49 (mannose); 6.29-7.90 (aromatic protons)
97	3.24, 2.97, 1.51-1.65 (alkylamino groups); 2.69 (N-$(CH_3)_2$); 4.10-5.63 (peptidic CH's); 6.20-7.93 (aromatic protons)
98	5.59 (C_{27}-H); 5.11 (C_{26}-H); 6.28-7.94 (aromatic protons)
99	1.23-1.43, 1.52, 2.77, 3.13 (alkylamino groups); 4.12-5.53 (peptidic CH's); 6.20-7.91 (aromatic protons)
100	1.22, 1.48, 1.61, 2.98 (alkylamino groups); 2.71 (N-$(CH_3)_2$); 4.10-5.71 (peptidic CH's); 6.21-7.93 (aromatic protons)

TABLE VII (continued)

^{1}H-NMR spectra (δ, ppm) in DMSO-d_6

Compound	
91	0.83, 1.16; 1.36, 2.04 (acyl chain); 1.88 (acetylglucosamine); 2.97 (CH_2-pyridine); 3.49 (mannose); 7.12, 7.24 (pyridine)
92	0.84, 1.13, 1.35, 2.01 (acyl chain); 1.87 (acetylglucosamine); 1.25, 1.56 (alkylamino groups); 3.89 (CH_3-ester); 3.49 (mannose); 5.59 (C_{27}-H), 5.09 (C_{26}-H); 6.16-7.83 (aromatic protons)
93	2.51 (N-CH_3); 2.77 (N-$(CH_3)_2$); 3.51, 3.02 (alkylamino groups); 5.58 (C_{27}-H); 5.08 (C_{26}-H); 6.34-7.91 (aromatic protons)
94	2.76 (N-$(CH_3)_2$); 3.56, 3.02 (alkylamino groups); 4.10-5.62 (peptidic CH's); 6.29-7.91 (aromatic protons)
95	0.84, 1.14, 1.43, 2.05 (acyl chain); 1.88 (acetylglucosamine); 2.52 (N-$(CH_3)_2$); 3.48 (mannose); 6.32-7.89 (aromatic protons)

TABLE VII (continued)

^{1}H-NMR spectra (δ, ppm) in DMSO-d_6

Compound	
86	0.83, 2.00 (acyl chain); 1.88 (acetylglucosamine); 3.48 (mannose); 4.10-5.60 (peptidic protons); 7.90-6.34 (aromatic protons)
87	0.83, 1.07-1.55, 2.00 (acyl chain); 1.89 (acetylglucosamine); 1.07-1.55, 3.01, 3.21 (alkylamino groups); 2.28 ($N(CH_3)_2$); 3.47 (mannose), 5.57 (C_{27}-H); 5.07 (C_{26}-H);
88	0.84, 1.21-1.45, 2.16 (acetylglucosamine); 3.21, 2.98, 1.96, 1.21-1.45 (alkylamino groups); 2.08 ($N-(CH_3)_2$); 3.48 (mannose), 6.26-7.88 (aromatic protons)
89	0.87, 1.18, 1.35, 2.03 (acyl chain); 1.87 (acetylglucosamine); 2.98, 2.45, 1.38 (piperidine); 7.13 (benzyl); 3.49 (mannose)
90	0.87, 1.18, 1.33, 2.03 (acyl chain); 1.86 (acetylglucosamine); 2.97, 1.34 (piperidine); 3.48 (mannose); 6.19-7.89 (aromatic protons)

TABLE VII (continued)

^{1}H-NMR spectra (δ, ppm) in DMSO-d_6

Compound	
80	0.84, 1.05-1.26, 1.33, 1.99 (acyl chain); 1.88 (acetylglucosamine); 3.70, 3.01, 1.48 (alkylamino groups); 3.49 (mannose); 5.59 (C_{27}-H); 5.10 (C_{26}-H); 6.29-7.90 (aromatic protons)
81	0.85, 1.23, 1.41, 2.05 (acyl chain); 1.90 (acetylglucosamine); 3.02, 1.51 (alkylamino groups), 2.72 ($(CH_3)_2$-N); 3.48 (mannose); 6.30-7.92 (aromatic protons)
82	0.84, 1.18, 1.38, 2.05 (acyl chain); 1.89 (acetylglucosamine); 1.58, 2.24, 2.72, 3.12 (quinuclidine); 3.48 (mannose); 6.30-7.92 (aromatic protons)
83	1.86, 2.24, 2.71, 3.16, 3.51 (quinuclidine); 4.10-5.85 (peptidic CH's); 6.21-7.87 (aromatic protons)
84	1.34-1.58, 2.69 (alkylamino groups); 4.07-5.68 (peptidic CH's); 6.21-7.85 (aromatic protons)
85	0.84, 1.19, 1.38, 2.05 (acyl chain); 1.88 (acetylglucosamine); 3.48 (mannose); 4.12-5.60 (peptidic protons); 7.92-6.33 (aromatic protons)

TABLE VII (continued)

^{1}H-NMR spectra (δ; ppm) in DMSO-d_6

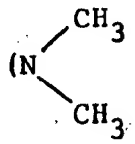
Compound	
75	0.83, 1.13-1.22, 2.03 (acyl chain); 1.87 (acetylglucosamine); 2.90, 2.74 (); 5.70-4.10 (peptidic CH's); 7.90-6.20 (aromatic protons)
76	0.84, 1.04-1.25, 1.43, 2.02 (acyl chain); 1.88 (acetylglucosamine); 1.24, 3.48 (ethyl group); 1.86, 2.95 (pyrrolidine); 3.68 (C_{12}-N); 5.58 (C_{27}-H); 5.09 (C_{26}-H); 6.31-7.88 (aromatic protons)
77	0.84, 1.18, 1.39, 2.05 (acyl chain); 1.89 (acetylglucosamine); 2.45, 3.65 (morpholine); 3.48 (mannose); 5.58 (C_{27}-H); 5.09 (C_{26}-H)
78	3.89, 2.92 (morpholine); 3.65, 3.20, 2.21 (alkylamino groups); 4.10-5.63 (peptidic CH's); 6.30-7.92 (aromatic protons)
79	1.23, 3.48 (ethyl group); 1.85, 2.95 (pyrrolidine); 3.64 (CH_2-N); 4.12-5.62 (peptide protons)

TABLE VII (continued)

^{1}H-NMR spectra (δ, ppm) in DMSO-d_6

Compound	
69	0.83, 1.13-1.22; 2.03 (acyl chain); 1.90 (acetylglucosamine); 3.48 (mannose); 5.60 (C_{27}-H); 5.10 (C_{26}-H); 6.30-7.90 (aromatic protons)
70	0.89, 1.17, 1.50, 2.08 (acyl chain); 1.88 (acetylglucosamine); 2.53 CN-CH_3); 2.28 (N-$(CH_3)_2$); 3.50 (mannose); 5.58 (C_{27}-H); 5.10 (C_{26}-H); 6.28-7.90 (aromatic protons)
71	0.83, 1.09-1.24, 2.03 (acyl chain); 1.93 (acetylglucosamine); 3.70 [(COO)CH_3]; 5.63 (C_{27}-H); 5.08 (C_{26}-H); 6.20-7.90 (aromatic protons)
73	1.39, 1.53, 1.75, 2.52, 3.18 (alkylamino groups); 3.68 (methyl ester); 5.56 (C_{27}-H); 5.09 (C_{26}-H); 6.32-7.90 (aromatic protons)
74	0.81, 1.12-1.25, 2.02 (acyl chain); 1.88 (acetylglucosamine); 3.48 (mannose); 5.60 (C_{27}-H); 5.11 (C_{26}-H); 6.28-7.93 (aromatic protons)

TABLE VII (continued)

^{1}H-NMR spectra (δ, ppm) in DMSO-d_6

Compound	
32a	0.83, 1.13-1.22, 2.02 (acyl chain); 1.88 (acetylglucosamine); 3.48 (mannose); 5.60 (C_{27}-H); 5.11 (C_{26}-H); 6.30-7.90 (aromatic protons)
32b	0.83, 1.13-1.22, 2.03 (acyl chain); 1.90 (acetylglucosamine); 3.48 (mannose); 5.60 (C_{27}-H); 5.10 (C_{26}-H); 6.30-7.90 (aromatic protons)
32c	0.83, 1.13-1.22, 2.03 (acyl chain); 1.88 (acetylglucosamine); 3.49 (mannose); 5.60 (C_{27}-H); 5.11 (C_{26}-H); 6.30-7.90 (aromatic protons)
33	0.83, 1.14, 1.43, 2.02 (acyl chain); 1.89 (acetylglucosamine); 1.62, 1.85, 3.65 (alkylamino groups); 3.66 (methylester); 3.49 (mannose); 5.59 (C_{27}-H), 5.11 (C_{26}-H); 6.30-7.92 (aromatic protons)
66	2.3 (CH_2); 4.10-5.64 (peptidic CH's); 5.48 (C_{27}-H); 5.06 (C_{26}-H); 6.34-7.90 (aromatic protons)
68	0.83, 1.13-1.22, 2.03 (acyl chain); 1.87 (acetylglucosamine); 3.50 (mannose); 3.69 /(COO)CH_3/; 5.63 (C_{27}-H); 5.14 (C_{26}-H); 6.30-7.80 (aromatic protons); 7.33 and 5.00 (benzyl moiety)

TABLE VII (continued)

^{1}H -NMR spectra (δ, ppm) in DMSO-d_6

Compound	
27	0.84, 1.22, 1.43, 2.02 (acyl chain); 1.99 (acetylglucosamine); 5.7-4.15 (peptidic CH's); 6.29-7.91 (aromatic protons)
28	1.88 (acetylglucosamine); 3.48 (mannose); 3.30 (N-CH_2); 5.60 (C_{27}-H); 5.10 (C_{26}-H); 6.35-7.93 (aromatic protons)
29	1.77 (lysine CH_2); 2.07 (acetylglucosamine); 3.75-5.58 (peptidic and aromatic protons)
30	3.65 (N-CH_2); 5.43-4.03 (peptidic CH's); 7.81-6.34 (aromatic CH's)
31	3.07, 3.67 (CH_2 of the substituent), 4.10-5.63 (peptidic protons); 6.22-7.79 (aromatic protons)

TABLE VII (continued)

^1H -NMR spectra (δ, ppm) in DMSO-d_6

Compound	
21	3.66 (morpholine); 5.63 (C_{27}-H); 5.07 (C_{26}-H); 6.25-7.79 (aromatic protons)
22	3.59 (N-CH_2); 5.49 (C_{27}-H); 5.10 (C_{26}-H); 6.18-7.87 (aromatic protons); 8.84-10.01 (phenolic OH's)
23	2.78 (N-CH_3); 5.49 (C_{27}-H); 5.07 (C_{26}-H); 6.33-7.79 (aromatic protons)
24	3.30 (piperazine CH_2); 5.50 (C_{27}-H); 5.11 (C_{26}-H); 6.19-7.81 (aromatic protons)
25	3.60 (morpholine); 5.4 (C_{27}-H); 5.07 (C_{26}-H); 6.22-7.81 (aromatic protons)
26	0.84, 1.11-1.17, 1.42, 2.00 (acyl chain); 3.30 (N-CH_2); 5.69-4.06 (peptidic protons); 7.78-6.32 (aromatic protons)